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Cerebral Protection, Resuscitation, and Monitoring: A Look into the Future of Neuroanesthesia

BRUNO BISSONNETTE, MD, GUEST EDITOR

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CEREBRAL PROTECTION, RESUSCITATION AND MONITORING: A LOOK INTO THE FUTURE OF NEUROANESTHESIA

GUEST EDITOR

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FORTHCOMING ISSUES

December 1992

EMBOLISM AND ANESTHESIA
Levon M. Capan, MD, and Sanford M. Miller, MD,
Guest Editors

Embolism during anesthesia is one of the catastrophes with which an anesthesiologist must be fully conversant. There are many kinds of embolism (thrombus, air, fat, amniotic fluid, tumor, septic, foreign material), and therefore embolism can occur in widely diverse clinical settings and operations. This issue of the *Anesthesiology Clinics of North America* on "Embolism and Anesthesia" is important and unique because it covers the cardiopulmonary physiology of embolism and all its possible diverse forms in great breadth and depth in a clinically relevant manner in one well-edited text. The quality of this issue is guaranteed because of the clinical wisdom and insight of the guest editors, Drs. Levon Capan and Sanford Miller.

March 1993

NEUROMUSCULAR FUNCTION AND BLOCKADE
Brian L. Partridge, MD, *Guest Editor*

June 1993

ANESTHESIA FOR EAR, NOSE, AND THROAT SURGERY
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Alan N. Sandler, MB, ChB, *Guest Editor*

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EPIDURAL AND SPINAL ANALGESIA AND ANESTHESIA: CONTEMPORARY ISSUES
M. S. Batra, MD, *Guest Editor*

December 1991

NEW DEVELOPMENTS IN PEDIATRIC ANESTHESIA
Jerrold Lerman, MD, *Guest Editor*

FOREWORD

The number of recent developments that have improved our ability to monitor, protect, and possibly resuscitate the central nervous system in such widely diverse conditions as acute stroke, postcardiac arrest, poor-grade cerebral aneurysm, spinal cord injury, and during the administration of neuroanesthesia has been enormous. These intellectual and practical advances make this subspecialty one of the most active and dominant in all of anesthesia, and it is no wonder, for example, that 10% of all American Society of Anesthesiology refresher courses at the 1991 and 1992 Annual ASA Meetings were devoted to this subject. Consequently, this issue of the *Anesthesiology Clinics of North America* on "Cerebral Protection, Resuscitation and Monitoring: A Look into the Future of Neuroanesthesia" is most appropriate and timely; the table of contents leaves no doubt it is clinically practical and relevant and intellectually exciting and stimulating.

The guest editor of this issue, Dr. Bruno Bissonnette, is a world-class neuroanesthetist and has outstanding clinical, teaching, and research qualifications. He is director of neurosurgical anesthesia and anesthesia research at The Hospital for Sick Children in Toronto, Canada and is widely respected for his clinical expertise with difficult neurosurgical cases, particularly in the pediatric patient. As a reflection of both his clinical and teaching expertise, he is an extremely sought-after speaker on both clinical and scientific subjects at national meetings. The word that best describes his research productivity is *incredible.* In the years between 1989 and 1992, for example, Dr. Bissonnette authored or co-authored 109 abstracts; as far as I know, this must be, or is close to, a world record. As might be expected from this clinical, teaching, and research profile, Dr. Bissonnette has been the recipient of numerous high honors and is an extremely well-funded researcher. In summary, because of the very timely and focused nature of "Cerebral Protection, Resuscitation and Monitoring: A Look into the Future of Neuroanesthesia" and the very high quality and very modern and up-to-date knowledge of the guest editor, this issue of the *Anesthesiology Clinics of North America* will be extremely valuable and interesting to all anesthesiologists.

JONATHAN L. BENUMOF, MD
Consulting Editor

CEREBRAL PROTECTION, RESUSCITATION AND MONITORING: A LOOK INTO THE FUTURE OF NEUROANESTHESIA

PREFACE

The last occasion that the *Anesthesiology Clinics of North America* devoted an edition to the subject of neuroanesthesia was 5 years ago. In the intervening period, the science of neuroanesthesia has continued its remarkable development. The number of published experimental and clinical studies has burgeoned and includes some of the outstanding advances in modern medicine. In the past, research in neuroanesthesia was largely restricted to studying the effects of anesthetic agents on the brain. Today, research has focused on such topics as energetics of cerebral metabolism, cerebral protection, cerebral resuscitation, and head injury. This issue describes these and other developments. It is not intended as a comprehensive review of the whole subject.

The neuroanesthesiologist has become an integral member of the neurologic team. The provision of excellent anesthesia in the operating room, although obviously of great importance, is but a part of the role. The management of new techniques in cerebral protection, resuscitation, and monitoring is equally important.

The mandate of each contributor was to review briefly the state of current knowledge in their subject and to stimulate the reader's curiosity by highlighting those aspects that they expect to be of interest to future researchers. Leading neuroanesthesiologists, each a recognized expert and authority in his and her subspecialty, have made this issue possible. As you reflect on the contents, I believe you will appreciate how effectively the contributors have fulfilled their mandate.

BRUNO BISSONNETE, MD
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CEREBRAL PROTECTION, RESUSCITATION, AND
MONITORING: A LOOK INTO THE FUTURE OF
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CEREBRAL PROTECTION AND NEUROANESTHESIA

Randall M. Schell, MD, and Daniel J. Cole MD

Following ischemic injury, the central nervous system (CNS) is limited in its regenerative ability. Accordingly, medical science has searched diligently for methods that ameliorate ischemia. In the process, neuroscience has suffered from episodes of scientific euphoria over animal studies and anecdotal reports of new methods of brain protection, followed by disappointment when the apparent limitations of these methods are applied in clinical trials. These methods include hypothermia, which has stood the test of time and developed a well-defined niche in the armamentarium of brain protection, barbiturates, for which the debate has covered the gamut of academic acceptance, and even an antitussive (dextromethorphan), which has been shown to have a neuroprotective effect.[90]

The distinction between protection and resuscitation is made by the time course of the therapeutic intervention. *Brain protection* has been defined as the "prevention or amelioration of neuronal damage evidenced by abnormalities in cerebral metabolism, histopathology or neurologic function occurring after a hypoxic or an ischemic event"[42] (i.e., a treatment that is instituted before and often sustained throughout the insult). *Brain resuscitation* refers to treatment that is begun after a brain insult to restore optimal brain function or limit secondary brain injury (see the article by Milde in this issue).

This article focuses on experimental and clinical brain protective strategies, realizing that any attending euphoria or disappointment should be tempered by the awareness that tomorrow's information may convey an alternative opinion.

From the Department of Anesthesiology, Loma Linda University, Loma Linda, California (DJC); and the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina (RMS)

CEREBRAL PHYSIOLOGY

The metabolic requirements of the brain fluctuate and are vitally dependent on continuous cerebral blood flow (CBF) for mitochondrial aerobic oxidation of metabolic substrate. Metabolism and CBF are not uniform throughout the brain (as expected from the fluctuating states of cerebral activity). However, changes in metabolism are associated with parallel CBF changes (the mechanism for flow-metabolism coupling is unknown, although local metabolic factors may have a central role[40]).

Approximately 60% of brain energy is used to sustain synaptic function as reflected in the electroencephalogram (EEG), with the remaining 40% required to maintain cellular integrity.[42] Although the brain constitutes only 2% of body weight, the high metabolic rate requires about 15% of the cardiac output. Normal cerebral metabolism ($CMRO_2$, 3.5 mL · 100 g^{-1} · min^{-1}) extracts about 20% of the oxygen consumed by the body from an average CBF of about 50 mL · 100 g^{-1} · min (Table 1).[18] With minimal metabolic reserves,[41] any interruption in CBF effects a rapid demise of brain tissue.

The large demand for blood and metabolic substrate is supplied by a conductive vasculature (internal carotid and vertebral arteries and their major tributaries) that supports a confluent network of nutrient arterioles and capillaries. The conductive system, or *circle of Willis,* is relatively fixed in caliber, with an inability to intrinsically respond to acute physiologic or metabolic needs. However, during specific states cerebrovascular resistance can change in the conducting vasculature. This system can develop extensive collateral channels that compensate and attentuate the effects of vascular occlusion on brain injury. Distal to the anterior, middle, and posterior cerebral arteries is the distributive microcirculation, which is the means for the final exchange of metabolic substrate with cerebral tissue. The distributive system has an incomplete anastomotic network, and it is at this level where CBF responds to the acute metabolic and physiologic needs of the neuron. The many factors that regulate CBF include the following:

1. $Paco_2$. Between 20 to 80 mm Hg, CBF varies directly by 1.0 mL · 100 g^{-1} · min^{-1} for each 1.0 mm Hg change in $Paco_2$.[83]
2. Pao_2. Within normal ranges CBF is not affected by Pao_2. However, below 50 mm Hg vasodilation occurs (overrides all other regulatory variables).[37] Minor degrees of vasoconstriction occur with hyperoxia.
3. Viscosity. CBF increases with decreasing viscosity (hematocrit).[87]
4. Perfusion pressure. Within a perfusion pressure of 50 to 150 mm Hg, CBF is constant. This property of autoregulation maintains a constant

Table 1. NORMAL PHYSIOLOGIC PARAMETERS FOR THE BRAIN

Global CBF	≈50 mL · 100 g^{-1} · min^{-1}
CBF (gray)	≈80 mL · 100 g^{-1} · min^{-1}
CBF (white)	≈20 mL · 100 g^{-1} · min^{-1}
CMR_{oxygen}	≈3.5 mL · 100 g^{-1} · min^{-1}
$CMR_{glucose}$	≈4.5 mL · 100 g^{-1} · min^{-1}
CBF/CMR_{oxygen}	≈15
Intracranial pressure	5–12 mm Hg
Venous Po_2	>35 mm Hg

Abbreviation: CMR = cerebral metabolic rate.

CBF by varying vascular resistance. (Cerebral perfusion pressure = mean arterial pressure − intracranial pressure or venous pressure).

PATHOPHYSIOLOGY OF CEREBRAL INJURY

Ischemic/anoxic, neoplastic, traumatic, inflammatory, or metabolic processes may be the initial insult resulting in global or focal cerebral injury. The focus of this section is on ischemia resulting from an absolute or threshold decrease in CBF to a specific area of the brain (the other topics are addressed in articles by Bickler, Milde, Archer and Priddy, and Skippen).

Ischemic damage may be the result of sudden occlusion of a major cerebral artery (e.g., carotid endarterectomy), global decrease in CBF (e.g., cardiac arrest), or a microembolus. A reduction in CBF below the threshold for cellular injury is the common mechanism of injury. The types of ischemia may be divided into focal (local decrease in CBF) or global (generalized reduction in CBF) ischemia. In focal ischemia, compensatory flow via collateral channels may limit the extent of infarction. However, such flow may also supply glucose to ischemic neurons that is anaerobically metabolized to lactate, resulting in profound acidosis and an extension of the original injury.[66] During global ischemia there is no collateral flow. In a normothermic brain, if flow and oxygen are not restored within 4 to 6 minutes irreversible neuronal damage occurs. Although duration of ischemia is a primary determinant of neuronal damage, other factors such as brain temperature and metabolism may be involved. In addition, there are selectively vulnerable regions of the brain (e.g., hippocampus) that are more sensitive to ischemia compared with the more resistant glial and vascular cells.[20]

When the cell demand for oxygen is greater than the supply, a series of events is initiated that if sustained result in a progression from cellular dysfunction to loss of cellular integrity and cell death. However, this is an oversimplification because other biochemical processes that are not dependent on the momentary interruption of oxygen (release of excitatory amino acids, free radicals, prostanoids) also take place. Because oxygen and ATP stores in the brain are meager, during conditions of inadequate oxygen supply oxidative phosphorylation ceases. Without ATP, active transport fails and the cell is unable to maintain normal transcellular ionic gradients. Consequently, neurons depolarize, lactate levels increase, protein and lipid metabolism is altered, and membrane degradation occurs.[59] In the event of reperfusion secondary mechanisms of injury such as free radicals, altered vasogenic edema, and delayed postischemic hypoperfusion may also contribute to the ultimate brain injury.

Cerebral Blood Flow and Brain Ischemia

The magnitude of reduced CBF and its duration are the primary determinants of ischemic injury and neurologic outcome. When CBF and oxygen supply is less than the metabolic needs of the cell, ischemia occurs. This threshold may be altered by anesthetic agents or physiologic changes. This concept is important, because CBF in a hypothermic brain during profound hypothermic circulatory arrest is zero, but because metabolic demands are low, the time before injury occurs is substantially delayed. In the absence of occlusive cerebrovascular disease, profound changes in CBF (decrease from 50–20 mL · 100 g^{-1} · min^{-1}) are required before there is evidence of neuronal dysfunction on the EEG. When CBF decreases to about 15 mL · 100 g^{-1} · min^{-1} EEG failure rapidly ensues. (Synaptic function is the first area of dysfunction as the remaining energy is conserved to maintain cellular homeostasis.) Between a CBF of 6 to 15 mL · 100 g^{-1} · min^{-1}, although the neurons are in jeopardy, a *penumbral* state transpires (that area of the brain for which CBF is adequate for prolonged cellular integrity but insufficient for synaptic function). If CBF is reestablished during the penumbral state neuronal function is reestablished. If CBF is less than 6 mL · 100 g^{-1} · min^{-1}, rapid and irreversible neuronal damage occurs.[18]

Cerebral Energy Changes and Ionic Homeostasis

As the energy reserves of the brain are limited, if CBF is interrupted for even a short period, ATP depletion occurs, which triggers a complex series of biochemical events. There is a loss of Na^+-K^+ ionic gradients when the calcium regulation of ATP-dependent transport mechanisms fails and ions shift across their gradients. With intracellular ionic shifts osmotic equilibrium (cytotoxic edema) is established, which leads to neuronal death and terminal depolarization of the neuron.[28, 54, 79] When the neuronal membrane is depolarized, voltage-sensitive Ca^{2+} channels open and an influx of Ca^{2+} occurs. This intracellular uptake of Na^+,Cl^-, and water leads to physical disruption of the membrane and is one mediator of ischemic damage.[69] However, it is the loss of Ca^{2+} regulation that may have a pivotal role in the evolution of neuronal injury.[80]

Calcium and Cerebral Ischemia

The entrance of calcium into cells is carefully regulated by voltage-operated calcium channels.[82] Calcium modulates the function of membrane channels, augments metabolism and ATP formation by influencing rate-limiting steps in the citric acid cycle, and alters the function of many enzymatic processes.[29] Intracellular concentrations of free calcium are normally maintained by extrusion from the cell, and sequestration into the mitochondria and endoplasmic reticulum via ATP-dependent mechanisms. During ischemia, intracellular Ca^{2+} increases, which activates phospholipases and hydrolyzes membrane phospholipids to free fatty acids (arachidonic acid). If oxygen is present (reperfusion or incomplete ischemia), these products may be oxidized to free radicals and prostanoids, which act to extend the primary injury.[83] Moreover, proteolysis, covalent modification of proteins, and disaggregation of the microtubuli lead to dysfunction of ion channels and receptors that inhibit axonal transport and contribute to increased membrane permeability, cellular degradation, and death.[59] Recently, the influx of calcium by agonist-operated channels that are gated by excitatory amino acids (glutamate and aspartate) has been implicated in ischemic neuronal injury.[78]

Excitotoxic Damage

There is evidence to suggest the *N*-methyl-D-aspartate (NMDA) receptor is in part responsible for ischemic cell injury. It is postulated that presynaptic release of excitatory amino acids (e.g., glutamate) activates the NMDA receptor and effects a postsynaptic influx of calcium.[11, 69, 81] The neurotoxicity of glutamate is associated with an effect on Na^+, Cl^-, water, and H^+ influx, which leads to neuronal swelling, dendritic osmolysis, intracellular acidosis, and activation of the NMDA receptor, with an extracellular to intracellular transmembrane flux of Ca^{2+}.[81] The evidence that supports excitotoxic damage includes the ubiquitous nature of glutamate and aspartate in the CNS, high concentrations of excitatory amino acids during ischemia and reperfusion, and the high density of NMDA receptors in selectively vulnerable areas of the brain and blockade of these receptors ameliorates ischemic damage.[12, 26, 81]

Intracellular Acidosis

Intracellular pH is normally regulated by removal of CO_2, oxidation of lactate, and transmembrane exchange of H^+ with Na^+. During ischemia, anaerobic metabolism occurs, producing lactate and cellular acidosis. With incomplete ischemia, plasma glucose and residual flow effect the magnitude of lactic acidosis. If glucose is supplied to the cells but oxygen is below the ischemic threshold, intracellular lactate will increase as glucose is anaerobically metabolized.[42] The following are proposed as the mechanisms of injury by acidosis: (1) inhibition of mitochondrial phosphorylation and energy production, (2) denaturation of proteins and nucleic acids, (3) glial swelling with microcirculatory compromise, and (4) increased release of Fe^{2+}, catalyzing the formation of oxygen radicals, leading to lipid peroxidation and membrane damage.[81]

Free Radicals

The participation of free radicals (chemical species with an unpaired electron) in ischemic neuronal damage has been difficult to prove. Free radicals are formed as the result of Ca^{2+} triggered cascades, acidotic reactions, and Fe^{2+} catalyzed reactions that damage membrane proteins and phospholipids. This damage occurs in microvessels, causing edema and infarction.[34, 59, 74] Further discussion is deferred to the article by Milde.

Proteins and Lipids

Without oxygen protein synthesis ceases,[9] and free fatty acids accumulate, which triggers the production of prostaglandins, thromboxanes, and leukotrienes.[62, 67]

Blood–Brain Barrier and Microvasculature

The endothelial cells of brain capillaries form a barrier that is impermeable to proteins and most polar solutes. Protein impermeability is maintained in the early period of ischemia. However, protein poor fluid enters neurons and glial cells by cytotoxic mechanisms. Depending on the severity of ischemia, breakdown of the blood–brain barrier (vasogenic edema) eventually occurs. In the event of reperfusion, protein-rich fluid crosses a disrupted blood–brain barrier, effecting an increase in ischemic cerebral edema formation.[65] Autoregulation is absent during ischemia and CBF is dependent on cerebral perfusion pressure.[42]

After temporary brain ischemia, injury may still occur via hypoperfusion deficits.

MODALITIES OF CEREBRAL PROTECTION

Brain protectants act at different facets of the ischemic cascade. Simplistically, they either increase oxygen delivery or reduce its demands or ameliorate pathologic processes (e.g., ionic fluxes, excitatory amino acids, free radicals) that are initiated during ischemia (Table 2).[54] To reach their full therapeutic efficacy, these strategies should be instituted before the onset of ischemia. However, by preventing secondary injury they are also useful after ischemia.

When contemplating cerebral protection modalities, both the duration and type of ischemia are important. With complete global ischemia, the duration of brain tolerance to ischemia (normothermia) is 4 to 6 minutes. Accordingly, if the cerebral protectant regimen extended the brain's tolerance for anoxia to 10 minutes; in theory any insult less than 10 minutes should be tolerated. In contrast, focal or incomplete ischemia may be permanent or temporary. In the event of permanent focal ischemia, if the protective regimen extended the tolerance to ischemia from 2 to 4 hours, but the ischemic insult were beyond the 4-hour limit, no real brain protection would be afforded. However, if focal ischemia is transient, cerebral protection may be relevant.

Physiologic Methods of Protection

Hypothermia

Hypothermia is currently employed during cerebrovascular surgery (e.g., giant aneurysms), intracranial tumor removal, cardiopulmonary bypass, and circulatory arrest (e.g., congenital heart disease). The associated cardiac arrythmias that occur with deep levels of hypothermia necessitate the use of cardiopulmonary bypass. Accordingly, the routine use of hypothermia is usually limited to mild-to-moderate levels. The theory of brain protection is a reduction of cerebral metabolism by 7% for each 1°C decrease in body temperature. Although this mechanism for prolonging brain tolerance to ischemia is the most easily understood, other mechanism(s) are plausible. As previously discussed, brain metabolism has an electrophysiologic (60%) and cellular integrity (40%) component. Hypothermia proportionally decreases the rate of energy use associated with both of these components. Thus, in the absence of electrophysiologic function, hypothermia may still convey additional brain protection.[48] The most common application of hypothermia is during cardiovascular surgery. Profound hypothermia (about 18°C) allows an arrest time of

Table 2. METHODS PROPOSED AS PROTECTANTS AGAINST CEREBRAL ISCHEMIA

↓ ↓ Metabolism	↑ ↑ Microcirculatory Flow	↓ ↓ Secondary Injury	Other
Hypothermia	Hypertension	Glucose control	Vascular bypass
Barbiturates	Hemodilution	Calcium entry blockers	
Isoflurane	Anticoagulation	Excitatory amino acid antagonists	
Etomidate	Rheologic agents	Free radical scavengers	
Lidocaine	Opioid antagonists	Iron chelation	
Opioid agonists		Prostaglandin inhibition	
		Steroids	

60 minutes without neurologic dysfunction.[32] Hypothermia is also used (about 26–28°C) during cardiac surgery in conjunction with cardiopulmonary bypass. With the high incidence of embolic phenomenon during low flow and pressure, a protective effect of hypothermia is logical but unproven. Even mild hypothermia may effect an extremely beneficial result on brain injury.[38, 52] A recent study demonstrated that 3°C of hypothermia was markedly protective in a rat model of incomplete forebrain ischemia.[72] In contrast to the protective effect of hypothermia, even mild (39°C) hyperthemia (not uncommon in stroke patients) may be associated with a worsened neurologic outcome.[15] If these principles were considered clinically, it might be prudent to allow surgical patients at risk for cerebral ischemia to passively or actively cool to about 33°C during the period at risk. Conversely, hyperthermia should be avoided.

Glucose

Glucose regulation is a principle of cerebral protection. Hypoglycemic injury is obvious. However, hyperglycemic injury is less straightforward. A proposed mechanism of hyperglycemic injury is intracellular lactic acidosis resulting from anaerobic glucose metabolism, which facilitates secondary pathologic processes.[64] The influence of hyperglycemia on ischemic brain injury was initially observed in diabetic stroke patients, and animal models of hyperglycemic ischemia.[55] Experimental models of global ischemia have consistently demonstrated worsening of ischemia from hyperglycemia. However, the association between glucose and neurologic injury after focal ischemia has been inconsistent.[25, 35] Withholding glucose is suggested in clinical situations with the potential for cerebral ischemia. Although studies have suggested that even relatively small glucose loads (equivalent to 1 L of 5% dextrose) administered before ischemia may increase the neurologic insult,[17] the treatment for hyperglycemia in the setting of cerebral ischemia has not been established. Injudicious use of insulin might effect an increase in intracellular glucose and the resultant acidosis. Accordingly, at this writing, conservative management is recommended.

Blood Pressure

One aim in limiting focal ischemia is to increase regional CBF, and pharmacologic augmentation of blood pressure has been proposed to ameliorate ischemic injury.[39] Under normal conditions, CBF is regulated by local metabolic needs. However, during ischemia, autoregulation is impaired and CBF is pressure passive.[4] Increasing systemic perfusion pressure is postulated to open collateral vessels, effecting an increase in flow to the area of ischemia.[86] Hypertensive therapy has consistently decreased injury in a rat model of middle cerebral artery occlusion.[16] However, the clinical efficacy has yet to be systematically analyzed and guidelines for therapy have not been established. The risk of increasing cerebral edema and hemorrhage or precipitating myocardial ischemia may limit its use to brief periods. Induced hypertension in the treatment of vasospastic ischemic may be beneficial.[7]

Hemodilution

As hematocrit decreases, viscosity decreases and CBF increases. Hemodilution (hematocrit about 30%) improves flow and allows for additional oxygen delivery.[7, 13] Conversely, increases in hematocrit (>50%) decrease CBF.[88] Although the optimal hematocrit during focal cerebral ischemia is 30% to 35%, the data do not currently support routine hemodilution in the treatment of human stroke. However, hemodilution for vasospastic ischemia has been beneficial. The role of hemodilution as a method of cerebral protection from focal ischemia in the operating room has not been defined. Hemodilution is currently accomplished with colloidal solutions such as hydroxyethyl starch and albumin. Hemodilution with these agents causes a decrease in hematocrit and therefore oxygen content, limiting the degree of hemodilution that can be obtained. Blood substitutes that carry oxygen may have a role. Fluosol, a perfluorohydrocarbon, has the capacity to carry oxygen but side effects have limited its use. The role of hemodilution with artificial hemoglobin and macromolecules with the potential to seal a leaky blood–brain barrier after ischemia[73] is being investigated.

CO_2 and O_2

In the context of focal ischemia, normocarbia should be maintained. During ischemia, cerebral vessels vasodilate and lose both their reactivity to CO_2 and ability to autoregulate.[85] Induced hypercarbia would not be expected to further dilate these vessels and the absence of significant benefit in clinical studies has been confirmed. Moreover, hypercarbia has the potential to dilate nonischemic vessels and further divert CBF from ischemic areas.[36] Although hypocarbia has the theoretical potential of constricting nonischemic vessels and shunting blood to the area of ischemia, reducing CO_2 has not been effective in either clinical or laboratory studies.[46, 70] Hyperoxia offers the theoretical advantage of increasing tissue oxygenation; however, its benefit is undocumented, and is logistically limited.

Pharmacologic Methods of Protection

These methods of cerebral protection refer to an intervention instituted before and often sustained during a potential period of ischemia. These methods might increase collateral blood flow, block the formation of pathologic products or steps in the ischemic cascade, or reduce cerebral oxygen consumption during ischemia. The protective effects of barbiturates, particularly when administered before a period of temporary focal ischemia has been demonstrated by a number of investigators,[45, 56, 75, 76] resulting in their use as the prototype for protection.

Barbiturates

There are many proposed mechanisms by which barbiturates are thought to protect the brain from ischemia (blocking calcium channels, reduction of catecholamines, membrane stabilization, free radical scavenging, favorable redistribution of regional CBF, reducing metabolism, and reducing intracranial pressure).[51, 68, 94] The evidence does not support the use of barbiturates to protect the brain from global ischemia. However, the evidence for barbiturate use during focal ischemia is not as clear. There are many animal studies and anecdotal clinical reports that advocate the use of barbiturates to reduce brain injury during focal cerebral ischemia.[44, 45, 56, 75, 76] However, the clinical studies have not been as encouraging. The use of barbiturates in patients suffering from acute stroke has been disappointing and is limited by the respiratory and cardiovascular side effects.[1] As a whole, the evidence does not support the use of barbiturates for permanent focal ischemia. However, during transient focal ischemia there is clinical evidence in support of the use of barbiturate therapy. During cardiac surgery with cardiopulmonary bypass, there is a high incidence of embolization (focal ischemia). Barbiturates administered during open heart procedures using specific bypass techniques have protected against frank stroke.[60] The use of barbiturate coma for brain protection following head trauma has been disappointing. Because of unwarranted hemodynamic side effects, barbiturates should be titrated to EEG burst suppression. By this means, an unnecessary dose of barbiturates may be avoided that would provide no brain protection and only result in hemodynamic depression.

Calcium Entry Blockers

Altered Ca^{2+} homeostasis has a key role in ischemic brain injury. Increased intracellular and mitochondrial Ca^{2+} leads to activation of phospholipases, membrane damage, and other secondary mechanisms of injury. Interruption of this cascade would theoretically be protective. As neurons and vascular smooth muscle are disrupted by this intracellular influx of Ca^{2+}, calcium entry blockers could protect against ischemia by preventing Ca^{2+} influx into neurons and increasing CBF (vascular dilatation) to reversibly damaged neurons. The calcium entry blockers nimodipine, lidoflazine, and flunarizine have been the most extensively investigated. Studies using these agents for cerebral protection have been contradictory and inconclusive. Nimodipine has reduced the occurrence of neurologic deficits and death in patients with cerebral vasospasm following subarachnoid hemorrhage.[2]

Following global or focal ischemia there is a period of decreased cerebral perfusion (delayed postischemic hypoperfusion).[30, 89, 95] This period of hypoperfusion contributes to the final brain injury. Nimodipine, given before or after global ischemia, has ameliorated this state of hypoperfusion and improved neurologic outcome.[49] Whether improved CBF or some other metabolic function is the reason for improved neurologic outcome is not clear. Studies using nimodipine for the treatment of stroke (focal ischemia) have been promising. When administered before middle cerebral artery occlusion in rats, nimodipine has increased local CBF and reduced the extent of cellular damage.[53, 55] A similar decrease in infarct area has been demonstrated when nimodipine was administered after middle cerebral artery occlusion in rats[23] (the efficacy of postischemic treatment is uncertain[33]). A recent prospective, double-blind study of nimodipine given within 24 hours of the onset of acute stroke demonstrated improved neurologic outcome and reduced mortality in humans.[22] Although initial studies of nimodipine have been encouraging, until further definitive human studies are performed, the use of nimodipine as a cerebral protectant cannot be universally recommended.

NMDA Receptor Antagonism

The NMDA receptor is predominant in areas of the brain that are selectively vulnerable to ischemia. It is proposed that during ischemia, the NMDA receptor is activated by excitatory amino acids (e.g., glutamate), resulting in cell death. Moreover, evidence suggests that Ca^{2+} influx occurs by agonist-operated calcium channels gated by glutamate or other excitatory amino acids.[69, 82] Accordingly, blocking the action of excitatory amino acids at the NMDA receptor should ameliorate ischemic injury. Ketamine and MK-801 are two phencyclidine receptor agonists that cross the blood–brain barrier and act as noncompetitive NMDA receptor antagonists. Kyenuric acid is a broad-spectrum excitatory amino acid antagonist with competitive and noncompetitive NMDA antagonist effects. Dextromethorphan, a common antitussive agent, noncompetitively blocks the NMDA receptor. As ketamine increases metabolism and intracranial pressure, its use as an NMDA receptor antagonist is limited. However, dextromethorphan and MK-801, as well as other NMDA antagonists administered before transient global ischemia, have reduced ischemic injury.[24, 90] Pretreatment or administration of MK-801 after cerebral ischemia has attenuated injury.[61] However, the use of NMDA receptor antagonists for protection against excitotoxic injury in humans awaits further investigation.

Corticosteroids

Potential mechanisms by which corticosteroids have been proposed to exert a cerebral protective effect include prevention of membrane phospholipid breakdown, reduction of edema formation, and scavenging of free radicals.[27] Although several studies have suggested a protective effect of steroids for stroke,[79] the preponderance of clinical and laboratory studies have not demonstrated a protective effect of corticosteroids on ischemic injury.[3, 10, 31] Moreover, corticosteroid-induced increases in glucose may have a detrimental effect on brain injury following ischemia.

Free Radical Scavengers/Iron Chelation/Prostaglandin Inhibitors

In the presence of oxygen, free radical formation occurs as well as the release of pro-oxidant iron, which is a catalyst in free radical reactions. Free radicals increase lipid peroxidation, prostaglandin synthesis, and membrane damage.[96] Imbalances in various prostanoids may propagate a vasoconstrictive and platelet aggregation state that may contribute to the postischemic hypoperfusion syndrome.[42] By eliminating iron as a catalyst, decreasing free radicals by using free radical scavengers or enzymes that increase free radical metabolism, or by using prostaglandin inhibitors (indomethacin), postischemic reperfusion injury has been decreased in several laboratory models.

Anticoagulants

The use of anticoagulants during ischemia is based on their ability to interfere with thrombus formation. A thrombus may either be the cause of ischemia or result during low CBF states. The efficacy of anticoagulation therapy in preventing recurrent cardiac source emboli has generally been accepted. However, despite the absence of proven benefits and considering the complication of cerebral hemorrhage many still believe that anticoagulation has a role during thrombotic ischemia.

ANESTHETICS AND CEREBRAL PROTECTION

Isoflurane

Isoflurane-volatile anesthetics produce a dose-related decrease in metabolism and increase in CBF. Clinically, isoflurane is unique among volatile anesthetics as it affects an isoelectric EEG at a concentration of 2.0 MAC.[57] Like barbiturates, isoflurane reduces that part of metabolic activity that is associated with electrical activity on the EEG. Although the neurophysiologic characteristics of isoflurane suggest a possible neuroprotective effect, do they translate to a demonstrable beneficial effect on ischemic brain injury?

In a study of over 2000 carotid endarterectomy procedures, Michenfelder et al[47a] noted that the critical CBF (the blood flow below which patients developed EEG evidence of ischemia) was lower for isoflurane (10 mL · 100 g^{-1} · min^{-1}) compared with enflurane (15 mL · 100 g^{-1} · min^{-1}) and halothane (20 mL · 100 g^{-1} · min^{-1}). They concluded that the ability of isoflurane to reduce the critical CBF was evidence of cerebral protection during transient incomplete regional ischemia. However, this study was retrospective, the anesthetic groups nonconcurrent, and neurologic outcome was not studied. Newberg et al[58] demonstrated a normal brain metabolic profile in a canine study of isoflurane-induced hypotension versus metabolic abnormalities in trimethaphan-, nitroprusside-, and halothane-induced hypotension.[47] In a primate model of focal ischemia in which isoflurane or thiopental were administered to EEG burst suppression, Milde et al[50] found no differences in neurologic and histologic outcome and concluded that isoflurane was protective. However, there was no control group in this study. More recently, Nehls et al[56] compared the protective effects of thiopental and isoflurane to a nitrous oxide/fentanyl control state in a baboon model of focal ischemia. They failed to demonstrate any protective effect for isoflurane when compared with thiopental. Gelb et al,[21] using a primate model of focal ischemia, found a protective effect with isoflurane. Ruta et al[71] studied the effects of either 1.2 MAC halothane or isoflurane on focal ischemia in anesthetized rats and found no difference in the extent of histochemical injury. Warner et al[92] anesthetized rats with 3% to 4% inspired isoflurane (EEG suppression) during a forebrain ischemic insult and found no neuronal protective effect of isoflurane relative to a nitrous oxide control group. Finally, the potential neuroprotective effect of isoflurane was studied by Sano et al.[72] They anesthetized rats with either 1.3 MAC isoflurane (normothermia), 1.3 MAC halothane (normothermia), or 1.3 MAC halothane with a 3°C temperature decrease (hypothermia) in a model of temporary incomplete forebrain ischemia. Histopathologic injury was assessed after a 3-day survival period. Isoflurane (normothermia) had no cerebral protective effect relative to halothane (normothermia) controls. In stark contrast, only 3°C of hypothermia markedly attenuated ischemic brain injury in the 1.3 MAC halothane group.

The possibility of isoflurane causing cerebral *vasodilation* in nonischemic areas of brain, and producing an intracerebral steal under conditions of regional incomplete ischemia has been suggested as an explanation for the failure of isoflurane to protect the brain. Furthermore, previous failures have also been attributed to the severity of ischemia. In this circumstance, metabolic activity would be absent due to the injury, and no further suppression or brain protection would be afforded. Although isoflurane has demonstrated neuroprotection in some models, its relative value as a method of cerebral protection from ischemia is placed in perspective by dramatic protection conveyed by 3°C of hypothermia when compared with isoflurane.

Lidocaine

In a dose-related manner, lidocaine reduces metabolism and at high doses (160 mg · kg^{-1}) abolishes EEG activity. In addition, Astrup et al[5] demonstrated that, like hypothermia, lidocaine reduces the metabolic rate (15%–20%) beyond

Table 3. SUGGESTED CEREBRAL PROTECTION REGIMENS FOR VARIOUS CLINICAL SITUATIONS

	Hypothermia	Barbiturates	Isoflurane	Ca^{2+} Channel Blockers	Hypertension	Hemodilution	Other
Carotid surgery	Mild	Consider	No	No	↑ 20%–30%	Consider	Vascular shunt, anticoagulation
Circulatory arrest	Profound	Consider	No	No	Consider during recirculation	Yes	—
Vasospasm	Consider	Consider	No	Yes	↑ 25%–35%	Yes	Early surgery
Head trauma	Consider mild	Consider	No	No	No	No	ICP control
Cranial tumor	Consider mild	Consider	No	No	No	No	—
Aneurysm/arteriovenous malformation	Consider all levels	Consider	No	Consider	Consider	Consider	—
Acute stroke	Consider mild	Consider	No	No	↑ 20%–30%	Consider	Vascular shunt, anticoagulation
Cardiac valvular surgery	Moderate	Consider(?)	No	No	Consider during postbypass	Consider	—
Coronary artery bypass graft	Consider	No	No	No	No	No	—

Abbreviation: ICP = intracranial pressure.

what is achieved with an isoelectric EEG. Indeed, the effects of lidocaine and hypothermia are additive. The mechanism of protection involves the blockade of neuronal Na^+ channels by (1) abolishing synaptic electrical activity and (2) reducing the energy required for maintaining ionic gradients by impeding Na^+/K^+ exchange.[6] The effectiveness of lidocaine is limited by its eliptogenicity and cardiotoxicity (doses used to produce an isoelectric EEG induce cardiac arrest). Despite the potential protectant effect of lidocaine, animal studies suggest that pretreatment with nontoxic doses of lidocaine is not protective.[77, 93] Lidocaine has been used to blunt the intracranial pressure response to embolic injury.[19] The use of lidocaine as a cerebral protectant is attractive but awaits further study.

Others

Etomidate is an intravenous agent that maintains a stable hemodynamic profile. It reduces metabolism and CBF similar to barbiturates. Because of its shorter duration of action, hemodynamic profile, and metabolic depressant effect, etomidate has been used with good results during temporary vessel occlusion for clipping of giant intracerebral aneurysms.[8] Animal studies regarding the neuroprotectant effect of etomidate are inconclusive.[84, 91] Further laboratory and clinical studies will delineate the role of etomidate as a neuroprotective agent.

Benzodiazepines reduce CBF and metabolism (to a lesser extent than barbiturates). In a quiescent brain, narcotics have little effect on CBF and metabolism. However, narcotics may decrease CBF and metabolism if given during arousal. Hemodynamic stability and ease of reversal make narcotic anesthetic techniques desirable. Narcotic antagonists (e.g., naloxone) have been used in the treatment of experimental ischemia with mixed results.

SUMMARY

There are no absolutely proven methods of cerebral protection for all circumstances of cerebral ischemia (Table 3). In general, maintaining adequate perfusion pressure and avoiding hyperglycemia would be the most relevant to the anesthesiologist. All other modalities should be a clinical judgement based on the risk-to-benefit ratio for that individual patient. Table 3 is a composite of additional cerebral protective modalities based on our opinions for several clinical scenarios. It is not meant to be definitive or conclusive, but a summary of our synthesis of data at this writing.

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CRANIOTOMY AND THE POSTERIOR FOSSA

Teresa Slee Mayberg, MD, and Arthur M. Lam, MD, FRCPC

Of the three cranial compartments, the posterior fossa is the smallest. However, because of the numerous vital structures that are found in this compact space and the difficulty with surgical access, an operative procedure in the posterior fossa presents a unique anesthetic and surgical challenge that often requires special considerations and monitoring. The focus of this article is to review the relevant issues concerning anesthesia for posterior fossa surgery.

ANATOMY OF THE POSTERIOR FOSSA

The anterior aspect of the posterior fossa is defined by the dorsum sellae and the basilar portion (the clivus) of the occipital bone. Laterally, the walls of the posterior fossa consist of the petrous portions of the temporal bones. The tentorium cerebelli and the squamous portion of the occipital bone make up the superior and posteroinferior aspects. Within the limits of the posterior cranial fossa (PCF) are contained portions of all the cranial nerves and their nuclei (with the exception of cranial nerves I and II), the cerebellar hemispheres, brain stem (pons, medulla), and the fourth ventricle. The third (oculomotor) and fourth (trochlear) cranial nerves arise from the midbrain. The oculomotor nerve emerges at the upper border of the pons, while the trochlear nerve exits from the dorsal surface of the brain stem. The pons is found in the most anterior portion of the posterior fossa and the fifth (trigeminal) cranial nerve is the only nerve arising from it. The remaining seven cranial nerves emerge from the medulla. Given the diversity of physiologic functions these structures

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perform, patients with disease pathology in PCF may present with a wide range of signs and symptoms.

CONGENITAL MALFORMATIONS

The symptoms of patients with Arnold-Chiari malformations are variable and somewhat dependent on the age of the patient at the time of initial presentation. During infancy and childhood, symptomatic patients are more likely to have a type II malformation (caudal displacement of cerebellar vermis, fourth ventricle, and lower brain stem below the foramen magnum). Infants and children may present with inspiratory stridor (10th nerve paresis), depressed gag reflex, aspiration pneumonia, episodic apnea, and upper extremity weakness. By contrast, patients with type I malformations (caudal displacement of cerebellar tonsils below the foramen magnum) are more likely to begin experiencing symptoms as adults. They may complain of headaches associated or exacerbated by Valsalva maneuvers. Pain that does not follow a dermatomal pattern may occur in the neck, shoulders, or arms related to associated syringomyelia. Bulbar symptoms are also possible, as is tethering of the lumbar spinal cord. In all age groups, regardless of malformation type, nystagmus, upper extremity weakness, or paraparesis may occur.[74] Surgical treatment typically entails a suboccipital craniectomy and in the case of a dural band, a C1 or C2 laminectomy may be required.

INTRA-AXIAL LESIONS OF THE POSTERIOR FOSSA

Cerebellum

Tumors involving the cerebellum frequently include (1) medulloblastomas, (2) cerebellar astrocytomas, (3) hemangioblastomas, and (4) metastasis. Medulloblastomas account for 4% to 10% of all primary brain tumors and 15% to 20% of central nervous system (CNS) tumors in patients under the age of 20 years. In general, medulloblastomas occur adjacent to the fourth ventricle in the midline, although approximately 10% can occur in the cerebellar hemisphere.[86] Typically children present with morning headaches, vomiting, and progressive ataxia, nystagmus, and occasionally cranial nerve palsies. Hydrocephalus is frequently a concomitant finding.[4]

Cerebellar astrocytomas account for between 10% and 20% of all childhood brain tumors.[63] These lesions are relatively benign, with excellent long-term survival after surgical resection. Usual presenting features are double vision, head tilting, or neck pain; hydrocephalus may or may not be present.

Hemangioblastomas are relatively common, histologically benign tumors. They can occur anywhere in the CNS, but most commonly are seen in the posterior fossa where they account for approximately 10% of all posterior fossa tumors.[83] Clinical symptoms tend to occur in the fourth decade, and the presentation varies with the location of the tumor. Lesions are most commonly in the vicinity of the fourth ventricle, but can occur at any location in the neuraxis. There is a frequent association with the von Hippel-Lindau complex, including visceral cysts and tumors, retinal hemangiomas, and polycythemia. Hemangioblastomas are extremely vascular, and preoperative embolization is usually desirable. Although these tumors are benign lesions, surgical treatment is directed toward total removal because hemangioblastomas have a tendency for recurrence, with cystic enlargement.[43]

Metastatic tumors are the most common posterior fossa lesions in adults. They usually affect the cerebellum although diffuse involvement of the meninges and brain stem may occur. These lesions are frequently associated with edema of the cerebellum and obstructive hydrocephalus. Surgical removal is indicated for most metastases producing mass effect in the posterior fossa.

Cerebellar hematomas are commonly associated with systemic hypertension in adults, although hemorrhage from metastatic tumors and arteriovenous malformations must be considered as well. Patients usually present with a deteriorating level of consciousness due to direct brain stem compression or hydrocephalus. Emergent ventriculostomy and evacuation of the hematoma can frequently provide an excellent outcome even in moribund patients.

Cerebellar infarction due to vertebrobasilar occlusive disease can present as a surgical emergency due to the expanding mass of infarcted tissue in the posterior fossa, producing brain stem compression and obstructive hydrocephalus. Emergent ventriculostomy and resection of infarcted cerebellar tissue is frequently a life-saving procedure.

Brain Stem

Gliomas are frequently found in the brain stem. Brain stem gliomas represent approximately 25% of all childhood intracranial tumors and are approximately equal in frequency to cerebellar astrocytoma and medulloblastoma. Gait disturbance and cranial nerve palsies are the usual presenting symptoms,[73] and hydrocephalus is rare. Diagnoses can usually be made without biopsy by radiographic appearance so surgery is not indicated in such a setting.

Fourth Ventricle

Tumors of the fourth ventricle include ependymomas and choroid plexus papillomas and carcinomas. Ependymal neoplasms represent approximately 5% of primary intracranial tumors,[25] the majority occurring in the first two decades of life. Approximately two thirds of ependymomas occur in the posterior fossa, usually in the midline, involving the floor of the fourth ventricle. Obstructive hydrocephalus is common. Complete removal is usually impossible owing to the involvement of the brain stem. Choroid plexus papillomas are more common in children, and the majority of these are located in the lateral ventricles. These lesions tend to hypersecrete cerebrospinal fluid, with associated communicating hydrocephalus. Choroid plexus carcinomas are more common in younger individuals and frequently invade the floor of the fourth ventricle.

EXTRA-AXIAL LESIONS OF THE POSTERIOR FOSSA

Cerebellopontine Angle

Cerebellopontine angle tumors include (1) schwannomas, (2) meningiomas, and (3) epidermoid and dermoid tumors. Schwannomas are benign neoplasms representing the most frequent extra-axial lesion in the posterior fossa. They can arise from a variety of cranial nerves, but most commonly are associated

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with the vestibular portion of the eighth cranial nerve (acoustic neuromas). The usual presenting symptoms are hearing loss, tinnitus, and a sense of imbalance. Total resection is feasible and usually involves a suboccipital craniectomy. With small tumors preservation of both hearing and facial nerve function is possible with the aid of intraoperative monitoring of seventh and eighth nerve functions.[31, 39, 75] Meningiomas arising from arachnoid cell rests in the dura of the posterior fossa can present in the cerebellopontine angle, over the clivus, or at the foramen magnum. The presentation depends on the location and involves either direct brain stem compression or cranial nerve deficits. Meningiomas are frequently vascular and preoperative embolization is indicated when feasible.

Epidermoids are uncommon tumors that usually present in middle age with symptoms related to local mass effect. Although these lesions can be located at many sites throughout the neuraxis, in the posterior fossa they are most frequently seen in the cerebellopontine angle. In contrast, dermoid tumors tend to involve the midline of the cerebellum, especially in young children with dermal sinus. Treatment for either lesion involves surgical removal when feasible.

Clivus

Lesions commonly affecting the clivus are (1) chordoma, (2) chondrosarcomas, and (3) carcinomas. Chordomas are derived from the primordial notochord and usually involve the dorsum sella or clivus in the posterior fossa.[50] They usually present with cranial nerve palsies because of intracranial extension or invasion of the cavernous sinus. These lesions can be approached ventrally by transseptal/transnasal or transoral routes.

Chondrosarcomas are malignant derivatives of chondrocytes that arise in the base of the skull adjacent to the clivus. These tumors are frequently invasive and usually present with cranial nerve deficits.

The proximity of the skull base to the perinasal sinuses and the oral and upper respiratory tract predisposes to direct invasion of the posterior fossa by carcinomas originating in these regions. In recent years, more aggressive approaches have been developed for these lesions, involving combined approaches using neurosurgery, otolaryngology and head and neck surgery, intraoperative radiation and brachytherapy, and associated revascularization procedures.

Arachnoid cysts are common congenital lesions affecting a variety of sites throughout the nervous system. In the posterior fossa, they are most commonly located in the region of the foramen magnum, cerebellopontine angle, or the pineal region.[84] Although often associated with headache, the majority of these lesions are asymptomatic. When associated with a mass effect, treatment involves marsupialization of the cyst, frequently with cystosubarachnoid shunting.

VASCULAR LESIONS

Approximately 15% of aneurysms are found in the posterior fossa. Aneurysms involving the upper basilar artery and superior cerebellar arteries are usually approached by a pterional or subtemporal approach, occasionally associated with splitting of the tentorium.[26] For those aneurysms in the lower and middle third of the basilar artery distribution, a lateral suboccipital approach is used, occasionally involving transsigmoid or presigmoid exposure. In certain settings, a transoral approach to ventrally situated lesions may be used, but is seldom used because of the risk of infection.[26]

Both arteriovenous malformations and cavernous angiomas can occur anywhere within the posterior fossa, but frequently involve the brain stem. The former has a significant rate of hemorrhage estimated at 2% to 3% annually.[27] In most cases, therapy for brain stem arteriovenous malformations involves radiosurgery, although embolization combined with direct surgical removal is feasible in certain locations.[27] Cavernous angiomas have a considerably lower rate of clinically significant hemorrhage (< 1% per year) and are frequently discovered as incidental lesions. Resection of brain stem cavernous angiomas is generally not attempted unless multiple hemorrhages have occurred. Cavernous angiomas are radioinsensitive.

Elongation of the vascular structures in the posterior fossa may impinge on susceptible cranial nerves. Those at risk include cranial nerves V, VII, VIII, IX, and X. The presenting symptoms depend on the nerve involved and may include trigeminal neuralgia (V), hemifacial spasm (VII), tinnitus or vertigo (VIII), glossopharyngeal neuralgia (IX), and hypertension (X). Microvascular decompression is usually reserved for those patients whose conservative medical treatment fails.

PREOPERATIVE ASSESSMENT

As with any patient scheduled for a major surgical procedure, a thorough medical history and physical examination focused on relevant organ systems are required, with particular emphasis on the cardiovascular, pulmonary, renal, and nervous systems. Of particular interest is a history of systemic hypertension because this can lead to alteration in cerebral blood flow autoregulation. Patients with ventriculoatrial shunts or known cardiac septal defects are at increased risk of venous or paradoxical air embolism, respectively, and are therefore not candidates for the sitting position. An autopsy study revealed that the incidence of probe patent foramen varied between 20% and 34%, depending on the age of the population studied. Younger subjects had a higher incidence than older subjects and the overall incidence was 27%.[37] Another study reported that a patent foramen ovale was demonstrable during a Valsalva maneuver using contrast echocardiography in 18% of young healthy patients.[54] Despite the potentially large population of asymptomatic patients with probe patent foramina, routine preoperative echocardiographic examinations are not recommended.[10]

In addition to standard pulmonary inquiries, patients presenting for posterior fossa surgery should specifically be asked about problems associated with sleep apnea, aspiration, dysphagia, recurrent pneumonias, and difficulties with coughing or clearing of secretions. These symptoms are often present in patients with brain stem pathology affecting the lower cranial nerves. Lesions affecting the brain stem and spinal cord may also cause significant muscular weakness and potential respiratory compromise.

Attention should be paid to neurologic symptoms, including mental status changes and symptoms of increased intracranial pressure, i.e., nausea, vomiting, and headache. Symptoms of cerebellar dysfunction include vertigo, nystagmus, and ataxia. Patients with acoustic neuromas generally present with the complaint of decreased hearing acuity, but larger tumors may cause other cranial nerve compression and dysfunction. Furthermore, depending on the pathology, patients with posterior fossa lesions may develop hydrocephalus and intracranial hypertension.

Because quadriplegia after craniotomies in the sitting position may in part be due to excessive neck flexion causing ischemia,[40, 95] the range of neck motion as well as the presence or absence of pain on flexion and extension should be documented. Motor deficits of any extremity should be noted. Neuromuscular blockade monitoring can be affected by such deficits and should be avoided in that extremity.

A history of past surgical or anesthetic problems, allergies, and current medications should be obtained. Special note should be taken of medications that may affect anesthetic management. Patients who have recently received intravenous contrast material or mannitol may be hypovolemic if the intravascular volume has not been adequately replaced. Anticonvulsant medications may increase nondepolarizer muscle relaxant requirements.[76]

In addition to standard preoperative laboratory studies, additional investigations should be guided by the patient's specific pathology. For instance, patients who would benefit from intraoperative evoked potential monitoring should have preoperative baseline studies. Alternatively, these may be obtained just before induction of anesthesia. Patients who present with respiratory muscle weakness should have as a minimal study, baseline negative inspiratory force measurements and arterial blood gas analysis to help guide postoperative airway management. In patients with vascular lesions (see prior section) preoperative embolizations are routinely performed. Occasionally, hemorrhage and cerebral infarction may occur during or after these procedures.

The patient's condition should be optimized preoperatively. The intravascular volume should be adequately replenished, and in patients with acute subarachnoid hemorrhage or significant cardiovascular disease, preoperative invasive monitoring may be required. Patients with increased intracranial pressure (ICP) secondary to tissue swelling should be treated with corticosteroids. Patients with marked hydrocephalus may require either preoperative ventriculostomy placement or ventriculoperitoneal shunting.[4] However, the latter is not without risk.[4, 94]

POSITIONING AND INTRAOPERATIVE CONSIDERATIONS

Common positions for posterior fossa craniotomies include the sitting, prone, and lateral positions. The lateral position is often modified to achieve the "park bench" position. It is possible to access the contents of the posterior fossa or the upper spine transorally with the patient in the supine position, but because of the risk of infection, it is seldom used for intradural lesions.[26] Therefore, the focus of this section is on the first three positions. Particular emphasis is placed on advantages and disadvantages of each position.

Park Bench and Lateral Positions

The park bench position is basically a modified lateral position, so named because the patient is positioned to resemble an intoxicated person reclining on a park bench.[45] The head and shoulders are positioned in varying degrees of rotation and lateral flexion, resulting in a modified brow-down posture. As with a true lateral position, a roll should be placed under the chest, caudal to the axilla of the dependent arm. Although the up shoulder is often retracted to improve surgical exposure, care must be taken to avoid excessive traction of the brachial plexus.

Disadvantages of this position include (1) potential peripheral nerve damage (2) macroglossia and neck swelling from venous outflow obstruction secondary to extreme neck flexion,[29, 62] although these complications are seen more often in the sitting position, and (3) possible spinal cord compromise, again from neck flexion. Extreme neck flexion also limits access to the airway and may cause the endotracheal tube to migrate or kink. Therefore, care should be taken to adequately protect pressure points, including the lower extremities. Extreme neck flexion should be avoided and the endotracheal tube position should be checked after final positioning.

The advantages of the park bench or lateral position over the sitting position include a decreased incidence of air embolism and positional hypotension.[17] Unlike the prone position, these positions allow ready access to the patient for purposes of monitoring. Furthermore, although controlled ventilation is routinely used to achieve hypocapnia to reduce cerebral blood volume intraoperatively, in rare instances involving basilar trunk or vertebral aneurysm where temporary or permanent feeding vessel occlusion is contemplated, spontaneous ventilation may be used as a monitor of brain stem well-being and is more manageable in the park bench than in the prone position.

Sitting Position

The term *sitting* is used to refer to patients placed in either a semirecumbent position, full sitting position, or anything in between. The patient is placed in the sitting position in the following manner. Following induction of anesthesia and placement of monitors, three-point pin fixation is applied to the head by the surgeon. Vaseline-impregnated gauze is wrapped around the pin sites, because these can be a site for air entrance.[13, 96] The legs are wrapped with elastic bandages, and an intermittent pneumatic compression stocking may also be used. The operating room table is then slowly flexed, with close monitoring of blood pressure to avoid the sudden occurrence of hypotension. Intravenous fluid loading may be necessary. The foot of the table should also be dropped so that the patient is placed in a semirecumbent position with the knees flexed. Neck flexion should be moderate and the chin should be at least two finger-breadths away from the chest during inspiration, and the tongue position should be checked to ensure that it is not protruding between the teeth. A soft small bite block rather than an oral pharyngeal airway is recommended. The arms are folded so that the hands rest on the lap. Pressure points are carefully padded, including the elbows and both lateral and medial aspects of the knees and heels.

The disadvantages associated with the sitting position include the possibility of air embolism, hypotension, quadriplegia, compressive peripheral neuropathy, orthopedic and dermatologic injuries, and macroglossia. Bilateral posterior compartment syndrome of the thighs has been recently reported as a rare complication of the sitting position.[81] Quadriplegia is a rare but devastating complication associated with the sitting position. It is postulated that impaired autoregulation of the cord caused by stretching it during neck flexion may place the patient at risk of ischemic spinal cord injury.[95] Alternatively, it may be caused by mechanical compression of the spinal cord in a patient with preexisting cervical stenosis.[40] Some authors advocate somatosensory-evoked potential monitoring during positioning in high-risk cases.[38, 64]

The major complication remains that of air embolism. This topic is reviewed in detail in the section entitled air embolism.

Prone

This is another alternative to the sitting position for surgical approach to midline structures in the PCF. After placement of the three-point skull fixation, the patient is carefully turned prone, with attention to head and spine alignment. Chest rolls extending from below the clavicles to the pelvis are placed such that the abdomen hangs free and the thorax is not compressed. The aim is to minimize mechanical distortion and allow normal respiratory excursion of the diaphragm. Arms are padded and tucked at the sides. Padding of the knees and ankles is performed such that there is modest flexion at each of those joints. The head is often positioned with the neck in flexion to improve surgical exposure. Again, extreme flexion should be avoided. The eyes must be carefully checked to ensure that there is no undue pressure on the orbits. The airway apparatus should be carefully inspected and secured.

Compared with the lateral position, the prone position allows better surgical access to the lower posterior fossa, cranial cervical junction, and the upper spinal cord. This is particularly true for midline lesions. The incidence of air embolism is less than that which occurs in the sitting position, but is not eliminated.[11]

The disadvantages of this position centered around its effect on pulmonary mechanics and intravascular resistance. Assumption of the prone position frequently increases airway pressures, particularly if the chest supports are improperly placed, leading to difficulty with ventilation. Obese or full-term pregnant patients are especially likely to suffer this complication.[17] The effect on the cardiovascular system includes a decrease in stroke volume and cardiac output associated with an increase in systemic vascular resistance. Furthermore, the placement of a precordial Doppler and efforts to monitor facial nerve function are nearly impossible in this position.

AIR EMBOLISM

Air entrainment occurs when a number of conditions are met. These include (1) venous pressure at the operative site that is below atmospheric pressure, (2) a vein that is open to the atmosphere, and (3) a vein that is kept from collapsing. Although air may be entrained whenever these conditions are met, it most commonly occurs during the first hour of surgery. During neurosurgical procedures, common sites of air entrainment include cranial diploic veins, emissary veins, and intracranial venous sinuses, which are kept from collapsing by their dural attachments. Entrainment can also occur from veins in the muscles as well as from the puncture site of the three-point head holder.[13, 96] The conditions for air entrainment almost always exist when a patient is placed in the sitting position, although air embolism may occur in patients undergoing nonneurosurgical procedures in other positions.

Studies reporting the incidence of air embolism vary considerably. Detection is largely dependent on the sensitivity of the monitors used. Early studies reported an incidence of 1% to 15%.[58, 66] Subsequent improvement in monitoring with introduction of the precordial Doppler has increased the reported incidence. Black et al[11] reviewed 579 cases for posterior fossa surgery in which 58%

of the patients were in the sitting position and the remainder were in a horizontal position. They reported that the incidence of venous air embolism (VAE) was significantly greater in the sitting position, 45% compared with 12%.

A number of studies have examined the mortality and morbidity associated with the sitting position and in general have found a relatively high incidence of air embolism but a low incidence of morbidity and mortality. A retrospective study of 488 patients reported a 6.8% incidence of air embolism, with an overall mortality of 2.5%. The incidence of air embolism was lower than in other studies but only 59% of the patients were monitored with a precordial Doppler.[87] A combined retrospective and prospective study of 554 patients undergoing surgery in the sitting position reported an associated morbidity and mortality of 1% and 0.9%, respectively.[60] The morbid events included two cases of VAE, two cases of hypotension, and one case each of paradoxical air embolus (PAE) and myocardial infarction. Patients who died succumbed to hypotension (two cases), VAE (one case), and PAE (one case), and one patient had become quadriplegic before death.[61] In the study by Black et al,[11] although they reported a significantly higher incidence of VAE in the sitting position compared with the horizontal position, they could not attribute any increased morbidity or mortality to VAE. Moreover, the incidence of hypotension (24% versus 19%, not significant), perioperative myocardial infarction (1.6% versus 0.3%, not significant), and blood requirement was higher in the horizontal position compared with the sitting position. Cranial nerve function was better preserved postoperatively in the sitting patients. This study also points out that, although the incidence of air entrainment is decreased during surgery in the horizontal position, it is not eliminated.

Cucchiara[19] reported that 3827 of his patients have undergone posterior fossa surgery or cervical laminectomies in the sitting position without any intraoperative death attributable to air embolism. One patient died from a pulmonary complication postoperatively that may have been related to an air embolism. Acute pulmonary edema following VAE has been reported by Chandler et al.[14]

There are several mechanisms by which air entrainment may adversely affect a patient. The rate of infusion, i.e., a rapid bolus versus a slow infusion, often determines the pathophysiologic effects.[2, 71] In dogs, a slow infusion initially caused an increase in pulmonary resistance, a decrease in peripheral vascular resistance, and an increase in cardiac output, resulting in a moderate drop in blood pressure. However, if the infusion continued, compensatory mechanisms were overwhelmed and severe systemic hypotension ensued. In contrast, a bolus injection resulted in a decrease in pulmonary vascular resistance and a profound decrease in cardiac output thought to be caused by an air lock in the right side of the heart. Both types of air entrainment caused an increase in central venous pressure (CVP). Holt et al[42] also documented the effects of air embolism in dogs. Following rapid, massive venous air injection (i.e., 3 mL/kg), near complete pulmonary obstruction occurred. The right-sided pressures became greatly elevated and right ventricular heart failure ensued. Left atrial pressure remained unchanged or decreased. There was practically no blood flow in the aorta.[42]

This increase in right-sided pressure[24] may cause air to pass from the right side of the heart into the left via a septal defect,[35] causing PAE. The pressure on the right side of the heart has been reported to increase merely by placing the patient in the sitting position.[79] In another experimental study, the discontinuation of positive end-expiratory pressure (PEEP) increased the likelihood of

PAE.[9] Anatomically, approximately 27% of patients have probe patent foramen ovale and are therefore potentially at risk for PAE in the event of air entrainment.[37] Functionally, 18% of patients exhibit right-to-left shunt during release of the Valsalva maneuver.[54] Additionally, there are reports of air reaching the systemic circulation without the presence of an intracardiac septal defect.[57] Although air has been detected in the systemic circulation without producing clinical symptomatology,[10] intracoronary air can lead to lethal arrhythmias and air in the cerebral circulation may have devastating neurologic consequences. Additionally, adverse pulmonary effects include pulmonary edema,[14] which may render the patient hypotensive and hypoxic.

Monitoring

Many systems are available for the monitoring of VAE, with varying sensitivity and specificity. Theoretically, the more sensitive monitors provide early warning signs, whereas less sensitive monitors may detect air embolus too late to allow successful treatment although the latter maybe more specific. The monitors are discussed in the order of increasing sensitivity as well as functional usefulness.

Clinical Signs

The sudden decrease in blood pressure, the occurrence of the characteristic "mill-wheel murmurs" (considered pathognomonic for air embolism), the development of arrhythmia, the sudden occurrence of gasping in a nonparalyzed patient, elevation of CVP, and retrieval of air from the CVP catheter are all consistent with air embolism. However, not only are these late signs, but with the exception of the mill-wheel murmur and retrieval of air from CVP catheter, they are also relatively nonspecific. More sensitive and specific diagnostic monitors are therefore necessary.

Sensitive and Functionally Useful Monitors

These include the use of the precordial Doppler and end-tidal CO_2 ($ETCO_2$) and end-tidal nitrogen (ETN_2) monitoring. The introduction of the precordial Doppler has greatly improved the detection of intracardiac air because it is much more sensitive then the previously mentioned modalities.[8, 32, 56, 60] Ideally, the Doppler probe should be placed along the right parasternal border to maximize audible signals from the right atrium. Occasionally, it has to be placed over the left parasternal border to obtain an audible signal. Proper placement may be verified by rapid injection of agitated saline.[90] The precordial Doppler can detect as little as 0.25 mL of intracardiac air.[56] The precordial Doppler, however, is not without limitations; use of cautery interferes with the recording and most units are equipped with cautery-suppression circuits, rendering the probe silent during surgical cautery. In addition, the signals become muffled or even lost during inspiration, particularly in patients with abnormal chest wall configurations (an increased anterioposterior diameter secondary to pulmonary disease). This obstacle can be overcome by using an esophageal Doppler probe. Muzzi and coworkers[72] compared the sensitivity of precordial versus transesophageal Doppler and found the former detected injected micro air bubbles 10% of the time compared with 100% of the time by the latter.[72] The transesophageal probe was equipped with a combination

Doppler sensor and an echocardiograph for confirmation of proper probe placement. In this study, the transesophageal echocardiographic probe also detected the incidence of micro air bubbles 100% of the time.[72] However, at the time of this writing, the use of the esophageal probe or transesophageal echocardiography is not yet cost effective and cannot be considered a practical monitor for VAE.

Monitoring of $ETCO_2$ has proved to be a useful, sensitive tool that complements the precordial Doppler for diagnosing VAE. An air embolus increases the alveolar dead space and decreases cardiac output, leading to an abrupt decrease in $ETCO_2$. To a certain extent the decrease in $ETCO_2$ quantifies the magnitude of the air embolus. However, it can also be nonspecific because any significant decrease in cardiac output regardless of etiology will produce the same finding. On the other hand, if the inspired gas does not contain nitrogen, during VAE the entrained air releases and expels nitrogen through the lungs and therefore can be detected by an abrupt increase in ETN_2. Experimental studies have indicated that significant changes in $ETCO_2$ and ETN_2 were detected with 0.25 mL/kg of injected air.[28, 61] Although the change in ETN_2 precedes the change in $ETCO_2$, sensitivity is not improved and extremely sensitive detection equipment is required.[28]

Useful Adjuncts

Another monitor advocated by some authors for use is the pulmonary artery catheter.[8, 59] Pulmonary artery pressure increases and pulmonary wedge pressure may decrease as CVP increases in response to a VAE. The additional information may help to identify patients at risk of developing a PAE. However, Matjasko et al[61] found that changes in pulmonary wedge pressure are less sensitive indicators then either changes in $ETCO_2$ or ETN_2. Moreover, due to the small size of the lumen, the pulmonary artery catheter is not a useful conduit for retrieval of air. Other monitors investigated include transcutaneous O_2 and CO_2 monitors.[33] However, development of hypoxemia from air embolism is a late event, and many conditions other than air embolism can influence transcutaneous CO_2; therefore, these monitors lack sufficient sensitivity and specificity for the intraoperative diagnosis of air embolism.

Advanced Monitoring

Transesophageal echocardiography is undoubtedly the most sensitive monitor for the diagnosis of VAE to date.[22, 33, 72] It allows visualization of intracardiac air and can detect a volume as little as 0.02 mL/kg. Unfortunately, the cost and technical expertise required has made its routine use for this purpose prohibitive at the time of writing.

Considering all the modalities available, the authors believe that in procedures in PCF where VAE is a potential risk, routine monitors should include a precordial Doppler, $ETCO_2$, and a properly placed CVP catheter (see following).

Treatment

Obviously, avoidance of air embolism is the best treatment. Meticulous attention to hemostasis and liberal application of bone wax will decrease the likelihood that the venous channel will remain open and therefore decrease the incidence of air entrainment. Although it has not been proved effective and its use remains controversial, some authors have proposed 10 cm H_2O of PEEP as a preventive measure against VAE (see following).

If air entrainment occurs, the anesthesiologist should immediately attempt to withdraw air through the central venous catheter[65] and treat any hemodynamic consequences while the neurosurgeon floods the surgical field with saline and looks for possible sites of air entry. Intravenous fluids, appropriate antiarrhythmic agents, and inotropic agents or vasopressors should be administered as needed. Hypoxia can also be a manifestation of an air embolism, and nitrous oxide can potentially increase the size of the embolus; therefore, inspired gas should be substituted with 100% oxygen. Should hemodynamic problems persist or if there is evidence of ongoing air entrainment, thought should be given to taking the patient out of the sitting position. Temporary jugular venous occlusion should also be considered. Animal data show that the lethal dose of injected air is doubled when the animal is positioned with the left side down.[42] However, this is rarely practical as a therapy once surgery is underway. In the event of complete cardiac collapse, the patient should be placed in the supine position as quickly as possible and closed chest cardiac massage[30] as part of advanced cardiac life support should be initiated.

To optimize retrieval of air following VAE, studies have analyzed types of CVP catheters as well as techniques of catheter placement. The usual sites of insertion include the basilic vein, the internal and external jugular veins, and the subclavian vein. Basilic vein insertion has been advocated by some because of its low complication rate and ease of placement.[5, 6, 20, 28] Its success rate, however, is lower than with internal jugular vein cannulation and considerable advancement of the catheter into the heart can occur with movement of the arm.[51, 82] Therefore, the authors prefer internal jugular vein cannulation. To effectively retrieve embolized air, proper atrial catheter placement is important. Bunegin et al[12] documented in a silastic heart model that the optimal position of the end of a multiorificed catheter was 0.5 cm beyond the sinoatrial node. Irrespective of the route used for the placement of the catheter, optimal position is best verified radiographically or electrocardiographically. This is particularly important when the basilic vein approach is used because the location of the catheter is less predictable than with other approaches. Electrocardiographic verification of the catheter position is achieved by attaching an isolated lead V to the saline-filled catheter, which is then advanced into the right side of the heart until the characteristic biphasic P waves are noted.

Multiorificed catheters have been found to be more effective than single-orificed catheters[12] in retrieval of air and are therefore preferred. Because the electrocardiogram likely arises from the proximal orifices, a predominantly negative rather than biphasic P wave should be sought during the placement.

As stated earlier, some authors have advocated the use of the pulmonary artery catheter as the catheter of choice in cases where air entrainment is a possibility.[8] A theoretical advantage is that air may be aspirated through the pulmonary artery port as well as from the right atrial port. However, standard pulmonary artery catheters have relatively small orifices, which limit aspiration even through the atrial port.[15]

Positive End-Expiratory Pressure

Controversy surrounds the use of PEEP for the prevention and treatment of VAE. Proponents advocate its use because it is thought to indirectly elevate intracranial venous pressure and therefore decrease the likelihood of air entrainment.[52, 93] Studying 24 patients in sitting position, Lee et al[52] reported a 26% incidence of VAE in 19 patients treated with 10 cm H_2O of PEEP as compared with 55% in five patients without PEEP. Voorhies et al[93] reported that in 81 patients treated with varying amounts of PEEP, air detection occurred in 50% of the cases. The morbidity in this series was 1%. These statistics are not different from those reported in series where PEEP was not routinely used.

Investigators who have actually measured superior sagittal sinus pressure found that 10 cm H_2O PEEP did not increase superior sagittal sinus pressure in children.[34] Zentner et al[98] measured the effect of PEEP on the transverse sinus pressure of patients undergoing posterior fossa surgery in the sitting position and reported that the addition of up to 15 mm Hg of PEEP had no effect on transverse sinus pressure. However, there was an associated decrease in mean arterial pressure.[98] Others have also reported a decrease in mean arterial pressure associated with the addition of PEEP.[78] Toung et al[92] also found PEEP to be ineffective in the animal model, whereas jugular venous compression was effective.

Another concern regarding the use of PEEP is the possibility that it may increase the incidence of PAE.[78] PAE may occur when (1) there is air in one of the right heart chambers, (2) a communication between the atrial or ventricular chambers exists, and (3) the pressure on the right side is greater than on the left. Therefore, a patient who has a probe patent foramen is theoretically at risk if the application of PEEP leads to a reversal of the normal left atrial–right atrial gradient. Cucchiara et al[23] demonstrated that in some patients with patent foramen ovale, right-to-left shunting occurred only when PEEP was used. Yet even preoperative echo testing may fail to identify patients at risk for PAE.[21] Moreover, others have shown that PEEP increases right atrial pressure and pulmonary capillary wedge pressure to the same extent and therefore the intraatrial pressure gradient remains unchanged.[9, 77, 97] As a preventive measure against the occurrence of PAE, administration of additional fluids as a means of increasing the patient's CVP has been suggested.[16] However, this has not been found to be of benefit experimentally.[11]

In summary, studies that have actually measured the effect of PEEP on intracranial veins, both in humans[98] and in animals,[92] have failed to document any beneficial effects on intracranial venous pressure. Furthermore, PEEP can cause a decrease in mean arterial blood pressure.[78] Given the lack of direct evidence that PEEP is useful in the prevention of air embolism, the authors do not advocate its routine use during sitting craniotomies. On the other hand, given the evidence that it does not in and of itself increase the likelihood of PAE, PEEP should be used if it is indicated for pulmonary reasons. Care should be exercised at the time of PEEP discontinuation because this has been associated with the occurrence of PAE.

ANESTHESIA FOR POSTERIOR FOSSA SURGERY

As the pathophysiology and surgical approach and requirements vary with the disease pathology, no one anesthetic technique can be advocated for posterior fossa surgery. The anesthetic plan should be goal oriented and developed by taking into account any preexisting disease states, presenting pathology, as well as constraints associated with the specific operation or positioning. Premedication should include continuation of drugs such as cardiac medication or antiseizure drugs. Steroid coverage, when indicated, should be provided preoperatively and intraoperatively. Anxiolytic premedication is usually reserved for patients with little or no neurologic symptomatology to avoid respiratory as well as mental depression.

Induction of Anesthesia

Generally speaking, the goals during this stage should be to preserve cerebral perfusion, avoid an increase in intracranial pressure, and institute monitoring appropriate for the surgical procedure or position. In addition to standard monitoring, which includes electrocardiography, noninvasive blood pressure, end-tidal CO_2, pulse oximetry, urine output, and temperature, direct intra-arterial blood pressure monitoring and placement of central venous catheters should also be considered routine monitoring for procedures in the posterior fossa. The authors prefer to place arterial catheters before induction of anesthesia in patients presenting for cerebral aneurysm surgery. As discussed in a following section, the nature and location of the pathology may necessitate the use of other monitors. The choice of anesthetic is not as crucial as the manner in which they are used or administered. In our institution induction of general anesthesia for posterior fossa craniotomy surgery is usually accomplished with thiopental, a narcotic such as fentanyl or sufentanil, and a nondepolarizing muscle relaxant. Succinylcholine can be used if there is no preexisting neurologic deficit. Although its effect on intracranial pressure and consequently its use in neuroanesthesia remains somewhat controversial, there is sufficient evidence to indicate that, provided there is adequate anesthesia, and pretreatment with metocurine is used, succinylcholine can be used safely.[89] Cooperative patients with mass lesions should be asked to hyperventilate before induction. Intravenous lidocaine, 1.5 mg/kg, is a useful adjunct to obtund the cardiovascular as well as cerebrovascular response to laryngoscopy and intubation. An induction regimen designed to avoid a hyperdynamic response is particularly important in patients with aneurysm. Low-dose isoflurane can be used to supplement the intravenous agents and provide hemodynamic stability, but should probably be avoided in patients with preexisting high ICP and cerebral ischemia.[36] If considered desirable because of its hemodynamic effects, isoflurane should be introduced with simultaneous hypocapnia.[1] A thiopental infusion at 4 to 5 mg/kg/h, with careful attention to systemic hemodynamic changes, may be more appropriate in this circumstance. Arterial and central venous cannulation are usually performed after induction of anesthesia, except in aneurysm surgery where we prefer to have direct blood pressure monitoring before induction.

To minimize the possibility of kinking and obstruction, a reinforced armored endotracheal tube is generally preferred. Oral airways are best avoided to minimize potential venous obstruction to the tongue and neck. A small soft bite block should be used instead. This is of particular importance if the facial nerve is to be monitored because the patient will bite down when stimulated.

Maintenance of Anesthesia

As with induction of anesthesia, no one particular anesthetic technique has been shown to be superior, and the maintenance regimen must be tailored to the needs of the patient and the requirement of the surgical procedure. The general aim is to provide a "slack brain" to reduce retractor pressure and to maintain adequate cerebral perfusion in a hemodynamically stable patient.

indicated, muscle paralysis is usually maintained with a agent guided with peripheral nerve stimulation. Mannitol, 1 th or without furosemide, 20 mg, is routinely given to reduce umbar drainage of cerebrospinal fluid is generally not necessary fossa surgery because of the proximity and therefore easy access al cisterns. Use of the sitting position further reduces this need. Some and perhaps controversial issues are briefly considered here.

avenous Agents Versus Inhaled Agents

The authors generally use a continuous infusion of narcotic supplemented with low-dose inhaled agents for maintenance. The dosage is usually chosen to be compatible with extubation and early awakening. In patients in whom immediate extubation is not a realistic goal, a shift can be made to an intravenous-based anesthetic from an inhaled-anesthetic.

Controlled Ventilation Versus Spontaneous Ventilation

While the superiority of controlled ventilation and the effectiveness of hypocapnia in reducing intracranial blood volume is undisputed and should be used in a great majority of the cases, there remains some rare cases where spontaneous breathing may have merits as a sensitive monitor of the brain stem well-being. Although most authors believe cardiovascular signs are equally sensitive, they are, however, less specific. These rare cases include aneurysms on the lower basilar trunk and verterbral arteries, particularly if temporary or permanent occlusion of the vertebrobasilar arterial system is contemplated.[45, 47, 48] With controlled ventilation, caution should also be exercised to avoid excessive hyperventilation. Whereas hypocapnia reduces cerebral blood flow and cerebral blood volume and consequently brain bulk, extreme hypocapnia can cause cerebral ischemia on its own. Arterial $Pa\text{CO}_2$ should therefore probably not be reduced to below 25 mm Hg.

Use of Nitrous Oxide

No definitive statement can be made regarding the use of nitrous oxide in posterior fossa surgery. Theoretically, nitrous oxide can increase the size of the air bubble should VAE occur and therefore should be avoided. Indeed, Munson and Merrick[70] demonstrated in dogs that the LD_{50} for bolus injections of air during nitrous oxide administration was one third the amount required during anesthesia where nitrous oxide was not used. However, a study in humans reported that the use of nitrous oxide did not alter the incidence of venous air embolism or hemodynamically significant events, providing that nitrous oxide was discontinued as soon as venous air was detected.[11] In addition, there is evidence in dogs that air embolism is better tolerated when the animal is breathing 100% oxygen as compared with 30% oxygen and nitrogen.[88] The authors routinely omit nitrous oxide when the sitting position is employed.

Special Monitoring Needs

Because of the proximity to the cranial nerves, operations on the lower brain stem and the cerebellopontine angle (Fig. 1) are associated with a significant risk of cranial nerve damage in addition to potential injury to the brain stem. Stimulation of the various cranial nerves also give rise to cardio-

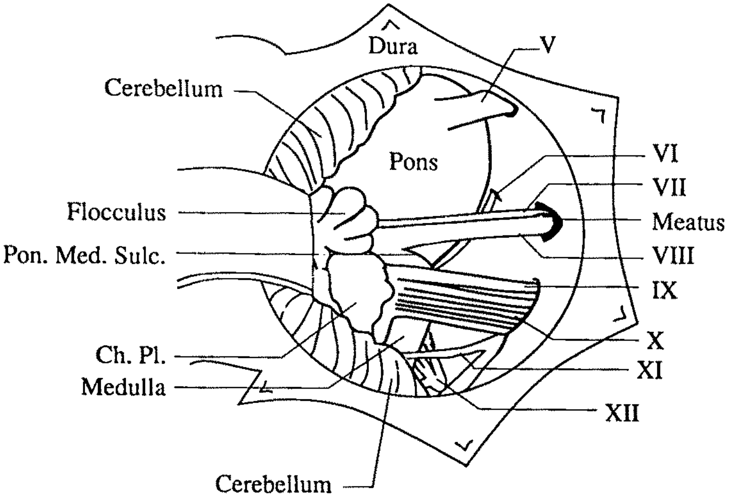

Figure 1. Surgical anatomy of the cerebellopontine angle illustrating the proximity of the lower cranial nerves to the pons and medulla. Ch. Pl. = choroid plexus; Pon. Med. Sulc. = pontomedullary sulcus.

vascular and respiratory reflexes not commonly seen in supratentorial surgery,[3, 6] for instance, tachycardia and hypertension from V, bradycardia and arrhythmia from X, and cough reflex from IX. To prevent potential injury to the brain stem and preserve functions of the cranial nerves, monitoring of somatosensory evoked potential,[55] brain stem auditory evoked potential,[47, 48, 53, 80] and evoked electromyogram of V, VII, XI, and XII are frequently employed. Such monitoring has been shown to decrease damage to cranial nerves VII[39, 67, 68] and VIII.[31, 75] This, however, poses an anesthetic challenge because recording of electromyogram requires normal neuromuscular function and therefore omission of muscle relaxants, yet simultaneous somatosensory-evoked potential monitoring precludes the administration of high-dose inhaled anesthetics. Although the use of partial paralysis has been advocated by some,[41] the authors prefer to omit muscle relaxants completely and instead use low-dose isoflurane supplemented with a narcotic infusion (e.g., sufentanil at 0.3 μg/kg/h) as well as a lidocaine infusion (4–5 mg/kg administered over 30 minutes followed by 45 μg/kg/min). (See also the article by Lam on evoked potentials). Neuromuscular blockade may be reinstituted once surgical resection is complete, but is often not necessary with this regimen. The narcotic infusion should be discontinued about 60 minutes and the lidocaine infusion terminated about 15 to 20 minutes before the end of the surgical procedure to allow prompt return of consciousness and respiratory drive.

Intravenous Fluid

While overhydration should be avoided, fluid restriction is not advocated. Indeed, in cerebral aneurysm surgery volume expansion and induced hypertension may be necessary to overcome vasospasm.[44] Blood transfusion is seldom required until the hematocrit falls below 30%. Fluid and electrolyte replacement should be guided by filling pressures and periodic electrolyte determinations. Glucose-containing solutions should not be used because hyperglycemia can aggravate ischemic insults to the brain.[49]

Induced Hypotension

Extreme hypotension is now seldom employed during clipping of cerebral aneurysm, although mild-to-moderate hypotension remains useful for this purpose as well as during resection of vascular tumors or arteriovenous malformation to reduce blood loss. This technique, however, is contraindicated in patients with preexisting vasospasm. No ideal hypotensive agent exists and all commonly used agents are acceptable.[46] The authors prefer to use either sodium nitroprusside or deep isoflurane anesthesia when not otherwise contraindicated. In recent years, temporary occlusion of the feeding vessel instead of induced hypotension has become popular,[7] although its efficacy relative to induced hypotension has not been subjected to a randomized, controlled clinical trial. The administration of barbiturates or etomidate before the occlusion is often advocated to minimize ischemic damage, presumably on the basis of reduction in cerebral metabolic rate.[7]

Emergence and Recovery

Because of the potential risk of brain stem injury during posterior fossa surgery, the management of emergence must be a joint decision with the neurosurgeon, taking into consideration the patient's preoperative condition as well as intraoperative events. In previously neurologically normal patients with otherwise uneventful surgery, prompt awakening and extubation is indicated. Coughing and straining should be minimized and lidocaine administration (if not already used as a maintenance anesthetic) at the time of emergence is a useful adjunct for this purpose. Postoperative hypertension is not uncommon and treatment is dependent on the patient's medical history and the disease pathology. Aggressive treatment is usually not necessary with aneurysms or nonvascular tumor, but is mandatory for arteriovenous malformations and vascular tumors because hemorrhage into the posterior fossa can be immediately life-threatening. In a large number of patients, however, immediate extubation is not possible nor should it be planned because of respiratory compromise from loss of central drive or peripheral muscle weakness or loss of protective airway reflexes. It is prudent to leave these patients intubated and continue their management in the intensive care unit.

Although ICP monitoring from the anterior fossa does not always accurately reflect and may lag behind change in pressure in the posterior fossa, it is nevertheless useful in the postoperative management of these patients[18] and is frequently placed in our institution. Pneumocephalus is not an uncommon complication following posterior fossa surgery in the sitting position[91] and may be detected with continuous ICP monitoring. Direct ICP monitoring from the posterior fossa has also recently been reported, but its risk-to-benefit ratio remains to be established.[85]

In summary, operative procedures in the posterior fossa represents a unique anesthetic challenge. A thorough understanding of the patient's pathophysiology and the surgical needs as well as potential complications is essential to successful anesthetic management.

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ANESTHESIA AND THE SPINAL CORD

Takahisa Goto, MD, and Gregory Crosby, MD

Surgery on the spine and spinal cord is far more common than surgery on the brain, but it receives much less attention among anesthesiologists. There are probably several reasons for this, but one result is that information concerning the influence of anesthetic agents and techniques on neurologic outcome from spine surgery is meager. There is no doubt, however, that for the most common type of spine surgery (i.e., laminectomy for lumbar disk), the incidence of serious, preventable spinal neurologic complications is remarkably low, so there is little need to modify careful, routine anesthetic management because of a specific fear of harming the spinal cord. On the other hand, patients with an unstable cervical spine, cord compression, scoliosis, or who are about to undergo cross-clamping of the thoracic aorta are at substantial risk for perioperative spinal neurologic damage. This article considers the perioperative care of such patients by focusing on and emphasizing the underlying principles of spinal cord physiology rather than the details of drug selection, in part because there is no evidence that any particular anesthetic agent or technique is superior to others. The sections dealing with spinal cord monitoring and resuscitation are intended to supplement more thorough discussions of central nervous system monitoring and protection elsewhere in this volume, and problems associated with chronic spinal cord injury are not reviewed. Instead, we have concentrated on clinical situations in which the spinal cord is vulnerable to injury, and perioperative management, though often controversial, may make a difference.

SPINAL CORD ANATOMY AND PHYSIOLOGY

Anatomy of Spinal Cord Blood Supply

The spinal cord has essentially separate anterior and posterior circulations, with both arising from the vertebral arteries and supplemented by intercostal

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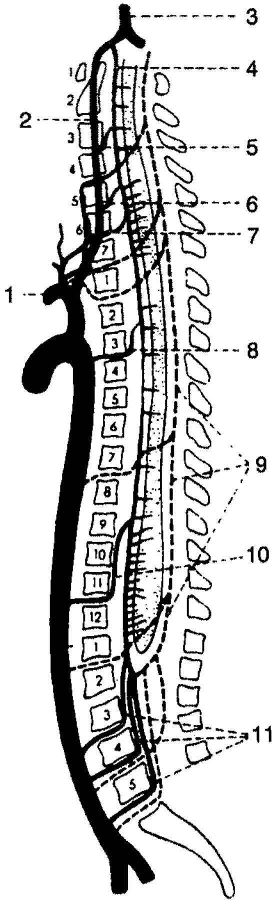
and lumbar vessels from the descending aorta (Fig. 1). The ventral two thirds of the spinal cord, which includes the corticospinal tracts and motor neurons, is supplied by a single anterior spinal artery. On the other hand, the dorsal one third of spinal cord parenchyma, which transmits sensations of proprioception and light touch, is supplied by paired posterior spinal arteries that actually form a plexus-like arrangement on the surface of the cord.[168] There is essentially no collateral flow between the anterior and posterior circulations, however.[168]

The anterior spinal artery is of greatest clinical importance because it supplies motor neurons and tracts. Some of its branches run circumferentially on the ventrolateral surface of the cord to supply white matter tracts, whereas sulcal branches penetrate the cord parenchyma and arborize in ventral gray matter (Fig. 2). The anterior spinal artery is of uneven caliber and not functionally continuous throughout its length, however. Thus, blood flow to the ventral spinal cord in some people is heavily dependent on collateral flow through radicular arteries arising from the aorta. These radicular vessels are



1 subclavian artery
2 vertebral artery
3 basilar artery
4 anterior spinal artery
5 ventral radicular artery (C_3-C_4)
6 ventral radicular artery (C_5-C_6)
7 ventral radicular artery (C_7-C_8)
8 ventral radicular artery (T_3-T_4)
9 posterior spinal artery
dorsal radicular artery
10 great ventral radicular artery
(Adamkiewicz's artery T_{11}-T_{12})
11 lumbosacral artery

Figure 1. A longitudinal view of the arterial blood supply to the spinal cord.

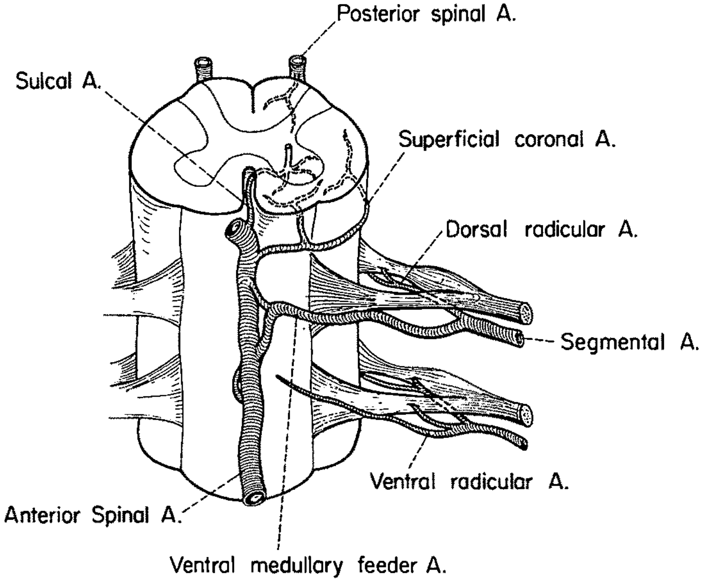


Figure 2. Cross section of the spinal cord illustrating blood supply through the anterior and posterior spinal arteries.

unpaired and typically arise from intercostal or lumbar arteries on the left side of the aorta. Only 6 to 8 of the 62 radicular vessels present during development persist into adult life, and 45% of the population has fewer than 5 (generally 1–2 cervical, 2–3 thoracic, and 1–2 lumbar). The large distance between these radicular vessels leaves watershed areas at the upper thoracic and lumbar levels where the spinal cord is particularly vulnerable to ischemia. For this reason, the great radicular artery of Adamkiewicz, which arises from the aorta between the eighth thoracic and third lumbar nerve roots and supplements flow to the ventral portion of the distal thoracic spinal cord and lumbar enlargement, is a particularly important collateral vessel (Fig. 1). Indeed, the location of the great radicular artery, which supplements flow to as much as 50% of the entire spinal cord in some individuals, may be a critical factor in determining the risk of spinal cord damage during surgery on the thoracic aorta (see the following discussion).

Physiology of Spinal Cord Blood Flow

Nearly all data concerning spinal circulatory physiology come from animal studies because acceptable methods of quantifying human spinal cord blood flow (SCBF) and metabolism do not exist. Recently, the velocity of blood flow within the anterior spinal artery[61] or microvasculature[126] has been measured using a Doppler technique, and the rate of blood flow inferred from these measurements correlates well with experimentally determined SCBF in cats.[126] However, technical difficulties, including those associated with maintaining constant probe contact with the spinal cord and extrapolating to flow from velocity (which requires knowledge of tissue blood volume), presently limit the experimental and clinical use of this technique. Nevertheless, animal data indicate that the spinal cord is controlled by the same factors and operates according to the same general physiologic principles as the brain,[83, 139] even though absolute rates of spinal metabolism and blood flow are lower. For instance, blood flow to spinal gray matter is about 50% that of cerebral cortex and flow to spinal white matter is lower still (about one third the rate of spinal gray matter).[171] Metabolic rates in the spinal cord are proportionally lower as well, so the ratio of supply to demand is probably similar to that of brain.

Regulation of Spinal Cord Blood Flow

Spinal Cord Perfusion Pressure. The concept of spinal cord perfusion pressure (SCPP) (SCPP = mean arterial pressure − extrinsic pressure on the cord) is clinically useful because it describes factors that affect the adequacy of spinal perfusion. Although there is a tendency to focus on blood pressure, other factors such as pressure exerted by local mechanical compression,[68] spinal venous congestion,[98] or elevated cerebrospinal fluid pressure (CSFP)[67] can be important determinants of SCPP in certain pathologic states. In fact, under most circumstances blood pressure is not a determinant of SCBF because spinal vessels maintain blood flow constant within a wide range of mean arterial pressure (MAP) by dilating or constricting.[74, 83, 139, 169] Studies are inconsistent with respect to the absolute limits of autoregulation; a range of 60 to 150 mm Hg is often quoted, but a lower limit of 45 mm Hg[169] and an upper limit of 180 mm Hg[74] have also been reported. If blood pressure exceeds these limits, autoregulation fails and SCBF becomes proportional to MAP. Similarly, conditions that produce maximal vasodilation (e.g., severe hypoxia or hypercarbia[65]) or abolish vessel reactivity (e.g., trauma[74, 182]) alter or eliminate the ability of the spinal circulation to autoregulate. Mild experimental cervical spinal cord injury, for example, reduces SCBF and shifts autoregulation to a higher range, while severe injury abolishes autoregulation completely.[74]

Extrinsic pressure on the spinal cord, which is difficult or impossible to monitor, can compromise SCPP despite a seemingly adequate MAP and may reduce SCBF if SCPP decreases below 40 to 50 mm Hg.[67] Examples of such extrinsic pressure might include cufflike constriction or mechanical compression of the spinal cord due to intraparenchymal or extramedullary spinal mass lesions, disk protrusion, spondylosis, bone displacement, or even surgical retraction. Epidural anesthesia and thoracic aneurysm surgery also increase CSFP and thereby may decrease SCPP. Administration of 10 to 20 mL of solution into the epidural space increases CSFP,[196] but this effect is transient and probably of little significance insofar as SCBF is concerned. On the other hand, the increase in CSFP that occurs when the aorta is cross-clamped reduces SCBF[192] and may contribute to the risk of paraplegia during thoracic aneurysm surgery (see section on Surgery of the Thoracoabdominal Aorta).

Pa_{O_2} and Pa_{CO_2}. Spinal cord blood flow responds to changes in Pa_{O_2} and Pa_{CO_2} much like the cerebral circulation. SCBF is unresponsive to oxygen tension until Pa_{O_2} decreases below about 60 mm Hg, when SCBF increases sharply.[65] Most, but not all studies, indicate that between 20 and 80 mm Hg Pa_{CO_2} there is a linear relationship between Pa_{CO_2} and SCBF,[65, 139] with an absolute change in SCBF of about 0.5 to 1.0 $mL \cdot 100\ g^{-1} \cdot min^{-1}$ per mm Hg change in Pa_{CO_2}.[171] In contrast, cerebral blood flow (CBF) changes approximately 1 to 2 $mL \cdot 100\ g^{-1} \cdot min^{-1}$ per mm Hg change in Pa_{CO_2}.[116] This difference in responsiveness probably reflects baseline differences in the absolute rate of spinal blood flow and CBF rather than differential sensitivities of the two vascular systems to carbon dioxide.

Effect of Anesthetics

Surprisingly little is known about how anesthetics affect spinal cord blood flow and metabolism, but it is reasonable to extrapolate from what is known about the effects of these agents on the brain. Thus, one would speculate that intravenous drugs (except perhaps ketamine) probably reduce SCBF and metabolism while volatile anesthetics are likely to reduce metabolism but increase flow. The few experimental data available indicate that this simple "rule of thumb" is qualitatively, if not quantitatively, valid. Nitrous oxide, for instance, increases both the spinal and cerebral metabolic rates 15% to 25% in paralyzed and mechanically ventilated rats, whereas pentobarbital decreases cerebral glucose utilization 50% but spinal metabolism of glucose only 10% to 20%.[34] Stimulation-evoked increases in spinal metabolic rate also appear relatively resistant to depression by barbiturates; somatosensory stimulation of pentobarbital-anesthetized rats increases glucose use substantially in the spinal cord but hardly at all in the brain.[33] Similarly, halothane produces greater metabolic depression in cortical and metabolically active subcortical regions of the brain (e.g., thalamic and auditory structures) than spinal cord.[32] On the other hand, both spinal cord and brain glucose use decrease almost 60% during propofol anesthesia.[22] Intrathecally administered local anesthetics seem to reduce spinal metabolism almost as much as general anesthesia with halothane or barbiturates.[31] One implication of the observation that spinal metabolism does not decrease as much as brain metabolism during anesthesia with halothane, pentobarbital, or intrathecal bupivacaine is that the protective action these anesthetics may have in spinal cord ischemia or trauma[18, 27, 170] is probably not metabolically mediated (see section on Resuscitation of the Injured Spinal Cord).

There are even fewer studies concerning the SCBF effects of anesthetics. Halothane and pentobarbital reportedly have similar effects on the spinal circulation of the dog,[64] even though they affect CBF in opposite ways. Whether these anesthetics increase or decrease SCBF is not established, however, because the study did not include unanesthetized animals.[64] Remarkably, the SCBF effects of isoflurane and enflurane have not been investigated. In addition to barbiturates, morphine is the only commonly used intravenous anesthetic for which data exist. The SCBF decreases about 25% when morphine is administered intravenously to halothane-anesthetized dogs but does not change when it is administered intrathecally, suggesting that morphine's SCBF effect is supraspinally mediated.[142] Subarachnoid local anesthetics do not have a uniform effect on SCBF. Subarachnoid lidocaine[107] and tetracaine[106] reportedly increase SCBF about 120% to 160%, whereas bupivacaine reduces it approximately 30%.[31, 105]

Intraoperative Monitoring of Spinal Cord Function

Despite apparently optimal surgical and anesthetic management devastating neurologic complications still occur during spine surgery, which explains the attractiveness and growing popularity of intraoperative monitoring of spinal cord function. There are now essentially three modalities for this purpose: the wake-up test, somatosensory-evoked potential (SSEP) monitoring, and more recently, motor-evoked potential (MEP) monitoring. A more exhaustive review of the subject is contained elsewhere in this volume.

The Wake-Up Test

The wake-up test is the traditional method for assessing spinal cord function during corrective procedures on the spinal column. Its main advantage is that it assesses anterior spinal cord (i.e., motor) function, but it does so only at one time point, is difficult to perform repeatedly, and is of little use for procedures such as cervical spine surgery and thoracic aneurysm repair. The wake-up test also requires patient cooperation and is difficult to perform on very young children or the mentally retarded. Risks of the test include emotional distress to the patient, dislodging of monitoring equipment, intravenous catheters, or spinal instrumentation, accidental extubation, and air embolism because negative intrathoracic pressures are generated during spontaneous ventilation. Although it is possible to use inhalational anesthetics when the wake-up test is planned, nitrous oxide-opioid-relaxant anesthesia is probably a more common choice because it usually provides a faster, smoother, pain-free awakening.

Somatosensory-Evoked Potentials

Perhaps because of the limitations of the wake-up test, intraoperative monitoring of evoked potentials, though still not routine, has become more common. Electrical potentials are generated within the neuraxis by stimulation of nerves such as the median at the wrist or the posterior tibial at the ankle, and the signal is recorded over the scalp or at various sites along the transmission pathway.[4, 69] The electrical signals are thought to arise from axonal action potentials and graded postsynaptic potentials during propagation of the impulse from the periphery to the brain.[70] These signals are weak compared with background electroencephalogram (EEG) activity, however, so computerized devices are necessary to average and summate hundreds of signals and extract them from background EEG. The amplitude and latency of each peak in the waveform tracing is recorded; comparing intraoperative recordings with a baseline obtained before spine manipulation is the way of identifying abnormalities.

Potentials may be recorded from electrodes positioned over the scalp (cortical SSEPs), the spinous processes, or in the epidural or intrathecal spaces (spinal SSEPs).[4] Spinal SSEPs have a few advantages over cortical SSEPs for intraoperative monitoring; they have higher amplitude and greater stability, which shorten signal acquisition time,[92, 128] and are relatively resistant to the effects of anesthetics. For example, epidural SSEPs are affected minimally by an end-tidal halothane concentration of 1.5% in humans,[129] whereas a similar dose markedly attenuates cortical SSEPs.[158] Indeed, one of the major difficulties with intraoperative SSEP monitoring is that many factors other than surgical manipulation interfere with recording and interpretation. Anesthetics and other drugs that act on the nervous system,[45, 46, 77, 104, 130, 145, 146, 157, 158, 173, 174, 175, 177, 180, 181] hypothermia,[110] hyperthermia,[47] hypotension,[78] hypoxia,[71] anemia,[152] and even surgical stimulation[178] may influence SSEPs, usually by decreasing amplitude and increasing latency. Intravenous anesthetics have minimal depressive effects. For example, although barbiturates prolong latency and decrease amplitude in a dose-related fashion, satisfactory SSEPs can be obtained after a dose large enough to produce burst suppression or isoelectricity on the EEG.[45, 46, 77] Fentanyl,[130, 146] even in the high doses used for cardiac anesthesia[174] and propofol[173] also permit reliable monitoring of SSEPs. Etomidate[104, 146, 181] and ketamine[175] actually increase amplitude transiently, and this property has been used to improve the quality of SSEP recording.[181] Inhalational agents, on the other hand, produce a dose-related decrease in amplitude and increase in latency. Nitrous oxide (50% in oxygen) causes as much as a 50% decrease in amplitude but does little to latency.[177, 180] The volatile anesthetics halothane, enflurane, and isoflurane produce qualitatively similar depressive effects on SSEPs, nearly abolishing signals at high concentrations.[145, 157, 158] Differences in the duration, intensity, frequency, or site of nerve stimulation among studies make it difficult to determine whether one inhalational agent is more compatible with recording of potentials than another. Moreover, the depression of evoked-potential signals by volatile anesthetics and nitrous oxide seems additive.[19] Accordingly, nitrous oxide-opioid-relaxant anesthesia is commonly advocated when SSEP monitoring is necessary, but potentials can be recorded reliably and successfully during anesthesia with a low dose of an inhalational agent. Perhaps of greater importance than the choice of anesthetic agents is endeavoring to maintain stable anesthetic and physiologic conditions during critical periods of the operative procedure; changing physiology and anesthetic depth can alter SSEPs and thereby potentially obscure detection of a critical neurologic event.

Intraoperative SSEP monitoring is widely, but not universally, accepted for corrective procedures on the spinal column, such as scoliosis repair and spinal fusion. It complements the wake-up test because it monitors function of another spinal pathway (i.e., dorsal columns) and, for practical purposes, does so continuously. The goal of continuous monitoring of SSEPs is to detect intraoperative events that would culminate in loss of spinal cord function early enough that corrective actions could be taken and a neurologic deficit averted. To date, however, only case reports and uncontrolled clinical studies support the view that SSEP monitoring during surgery actually serves this purpose.[58, 69, 70, 135, 199] The largest clinical study concerns 1168 consecutive orthopedic spine procedures (spinal fusion and instrumentation for deformity; 88% for scoliosis) performed under hypotensive anesthesia, in which SSEPs were measured by means of bipolar electrodes positioned in the epidural space approximately two levels above the vertebrae to be fused.[58] Technically adequate signals could not be obtained in 26 cases (2.2%). Greater than a 50% decrease in SSEP amplitude occurred in 119 patients (10%) on one or both sides during surgery, but the changes were transient and of no consequence in 35. Of the 84 patients with persistent SSEP changes, only 33 had neurologic complications; a decrease in SSEP amplitude of more than 50% and limited or absent intraoperative recovery of amplitude were identified as predictors of a postoperative neurologic deficit. There were no neurologic complications among those with normal intraoperative SSEPs or an SSEP amplitude consistently greater than 50% of normal (i.e., no false-negative SSEPs; 100% sensitivity). On the other hand, experience with intraoperative SSEP monitoring for cases involving intramedullary and extramedullary spinal cord lesions (e.g., tumor, arteriovenous malformation) or laminectomy surgery[135, 186, 199] is surprisingly limited. One small study[135] found that the velocity of impulse conduction across the operative field, calculated from SSEPs recorded from epidural electrodes placed above and below the operative site, accurately predicted postoperative neurologic improvement or deterioration in patients with spinal cord pathology such as tumors or arteriovenous malformations. Another study reported 26 consecutive cases, 17 of which were neurosurgical procedures on the spinal cord, performed with SSEP monitoring using either subdural or epidural electrodes above the operative site.[199] Among three patients with intradural spinal cord tumors, loss or deterioration of the SSEP waveform occurred in two and persisted despite corrective efforts; both patients had a new postoperative neurologic deficit. Thus, during surgery for intraparenchymal spinal lesions, SSEP recording may help identifying spinal injury but not enable the surgeon to prevent it.

Because SSEPs are conducted by the dorsal columns whereas motor neurons and tracts are in the ventral portion of the spinal cord, it is theoretically possible for a false-negative SSEP (i.e., postoperative motor deficit with preserved intraoperative SSEPs) to occur. Proponents of SSEP monitoring argue that isolated disruption of blood flow to the anterior cord is rare and compromise of SCBF is sufficiently global with most insults that SSEPs would be affected. In animals, cord compression reduces evoked potential amplitude regardless of whether it is applied ventrally or dorsally.[5] In addition, transmission of SSEPs may not occur exclusively in the dorsal columns; pathways that partially reflect anterior spinal cord function may also contribute to the signal.[23, 24, 92, 162] In any case, only a few anecdotal reports of a severe postoperative motor deficit following normal intraoperative SSEPs exist.[62, 120] In contrast, false-positive SSEPs are both common and problematic because they may lead to unnecessary interventions, incomplete surgery, or desensitization of the surgeon to warnings of significant change. In the large study[58] of patients undergoing scoliosis surgery, for instance, 51 of the 84 patients with a persistent decrease in SSEP amplitude of greater than 50% were neurologically normal postoperatively and, therefore, represented false-positive studies. This false-positive rate (51/1168 total patients studied or 4.4%) is similar to that reported by one other study.[4]

These limitations of SSEP monitoring as well as the complexity and expense of the equipment, need for specially trained personnel, and low incidence of intraoperative neurologic injury for many spinal procedures probably explain why SSEP monitoring is still not a universal adjunct for such surgery.

Motor-Evoked Potentials

Because of concerns about the reliability of SSEP monitoring for detecting threatened motor function, MEP monitoring is appealing.[124] In practice, the motor cortex is stimulated by a transcranial electric current or, more recently, a pulsed magnetic field generated by a coil placed over the scalp.[136, 183] Electrical activity resulting from the discharge of cortical motor neurons is detected peripherally, with electrodes placed over the spinal cord or peripheral nerves, or by observing electromyelographic activity or movement in the appropriate region of the body.

Several animal studies suggest that MEPs are more sensitive than SSEPs for detecting spinal cord damage[123, 179] and correlate well with neurologic outcome following trauma[179] or overdistraction of the spinal cord.[156] Clinical experience is limited and uncontrolled,[99, 121, 204] but seems to suggest that MEPs may be better predictors of neurologic outcome than SSEPs when the two tests differ.[125] For example, patients who remained paraplegic after decompression and stabilization following thoracic spinal cord injury had somewhat preserved SSEPs but no detectable MEPs.[125] Intraoperative monitoring of 20 patients undergoing cervical spine surgery correctly predicted postoperative quadriplegia in one patient with complete loss of MEP and remission of symptoms in two patients whose MEP amplitude increased following removal of vertebral bone tumors. There were no false-negative studies and no patients with MEP amplitude attenuation of less than 50% had neurologic dysfunction.[99] However, if loss or persistent attenuation in MEP amplitude of greater than 50% is considered positive, there is about a 20% incidence of false-positive results during spinal surgery.[204] One significant limitation of this monitoring modality is that MEPs seem to be extremely sensitive to anesthetics.[60, 77, 94, 195, 205] Even 66% nitrous oxide or 0.5% isoflurane decreases MEP amplitude by 90% and 80%, respectively,[77, 205] and also prolongs latency substantially. Intravenous agents such as thiopental, fentanyl, and etomidate, though possibly less problematic, are not entirely devoid of effects on MEPs.[60, 195] Another theoretical concern is that repetitive electrical stimulation of the motor cortex of the brain could induce seizures either directly or through kindling, but no such complications have been reported, and cortical stimulation for MEP monitoring does not change the EEG.[13] Many more studies are necessary, however, before the limitations and value of MEPs in clinical practice are clear.

CLINICAL IMPLICATIONS AND APPLICATIONS

This portion of the review applies the information outlined previously in an effort to (1) provide a rationale for certain clinical practices, (2) identify and address controversies, and (3) offer suggestions for minimizing the risk of injury to the spinal cord during certain procedures. However, one must be aware that many clinical practices concerning anesthesia for the spine and spinal cord are based entirely on animal data or convention, and assurance that any particular tactic affects patient outcome is accordingly uncertain.

Surgery for Decompression of the Spinal Cord

Intraspinal and extraspinal lesions (e.g., herniated disks, spondylosis, primary or metastatic tumors, epidural hematomas or abscesses, and so forth) that compress the spinal cord and potentially produce local ischemia are probably the most common indications for spine surgery. Compression of the spinal cord will, to varying degrees, reduce SCBF,[172] produce interstitial edema and venous congestion,[97] and interfere with nerve impulse transmission.[68, 102] Consequently, maintaining perfusion pressure and/or reducing (or at least not exacerbating) cord compression are reasonable clinical management objectives.

Blood Pressure Control

The partially compressed spinal cord appears to be particularly vulnerable to a small decrease in blood pressure. For example, experimental studies suggest that moderate hypotension produces irreversible paralysis in the partially compressed but functionally intact spinal cord,[90] and minimal compression superimposed on hypotension decreases both SCBF and impulse transmission.[68] Clinical position-related complications such as midcervical quadriplegia and central cord syndrome (see section on Positioning) are often attributed partially to hypotension superimposed on compression,[84, 122, 141, 159, 201] without much evidence that this is the case. The fact that SCBF is not autoregulated and is likely to be reduced in the functionally intact but compressed cord[68, 97] may predispose to sensitivity to hypotension. Combined with the fact that anesthesia induction and adjunctive measures to improve compliance (e.g., hyperventilation) are not likely to improve SCPP, these observations provide some justification for concern about hypotension in the patients with compressed spinal cords. Thus, maintaining MAP at or above the patient's lowest recorded awake value is commonly advocated. Application of theory to practice is complicated by uncertainty as to how blood pressure affects SCBF and SCPP in a particular patient and by the fact that no controlled clinical studies have evaluated the role of hypotension in spinal cord damage.

Physiologic and Pharmacologic Decompression

Although deliberate hyperventilation to lower blood flow and osmotic diuretics to decrease water content are the two principal strategies for improving intracranial compliance and maintaining cerebral perfusion pressure, they are seldom discussed for spinal surgery. Perhaps the reason for this is that reducing CSFP may not benefit compressed segments of the spinal cord because local mechanical compression, rather than elevated CSFP, is likely to be the problem in most clinical conditions that require decompression surgery. Moreover, because vessels in the area of pathology generally lose responsiveness to CO_2,[182] hypocapnia is unlikely to reduce blood volume and decompress the cord locally. Similarly, although vasogenic edema of the spinal cord occurs after a variety of insults,[66] including compression,[97] it is probably not treated very effectively with mannitol because (1) osmotic diuretics require a permeability barrier to draw water out of the tissue, (2) the normal blood–spinal cord barrier is approximately twice as permeable as the blood–brain barrier to mannitol,[38] and (3) spinal compression and trauma often disrupt the blood–spinal cord barrier.[42] Whether these treatment modalities benefit the compressed spinal cord has not been formally tested, but neither hypocarbia nor hypercarbia prove superior to normocarbia with respect to recovery of motor function, normalization of SSEPs, or preservation of tissue histology,[89] and mannitol does not improve SSEPs[163] in models of acute experimental spinal cord injury.

Positioning

Positioning of the patient for spinal surgery is itself a complete topic, the details of which are beyond the scope of this article. Nevertheless, two aspects of patient positioning deserve consideration because they allegedly contribute to spinal neurologic injury.

First, the position of the neck during surgery is thought to contribute to postoperative neurologic dysfunction in patients with an already narrowed cervical spine. Central cord syndrome, for instance, has been described following neck hyperextension[159] and decompressive laminectomy,[122] presumably related to compression of the spinal cord by a buckled ligamentum flavum or "pinching" of the cord between the posterior elements of the vertebral body and the vertebral lamina.[40] Midcervical quadriplegia is another rare position-related complication that probably also requires preexisting narrowing of the spinal canal. This complication has been reported following procedures performed in the seated position,[84, 141, 201] and it is thought to be due to extreme hyperflexion of the neck, perhaps resulting in stretching and ischemia of the spinal cord. Hypotension is thought to predispose to both complications, although central cord syndrome has occurred without hypotension and despite apparently meticulous positioning and anesthetic management. Coincidentally, elevated intracranial pressure seems particularly harmful to cervical cord perfusion in the seated position; cervical and thoracic cord flow is 50% lower than normal in the sitting position if intracranial pressure is elevated, whereas flow to the lumbar cord is unchanged.[49]

Airway Management in a Patient with a Tight Cervical Cord

Exacerbated weakness, paresthesias, or pain during neck movement are often taken as clinical evidence of a "tight" cervical cord, and localized obliteration of the subarachnoid space or cord compression on computed tomography or magnetic resonance scanning confirms the suspicion. The optimal method of intubating a patient with such a tight cervical cord—awake versus asleep—is controversial. There is no question that spine movement occurs with airway maneuvers, but most of the movement during direct laryngoscopy in persons with a stable cervical spine occurs at the atlantoaxial junction while the lower cervical spine moves little.[88] This implies that except for pathology at C1–2, neck movement is unlikely to exacerbate or create a neurologic deficit. Indeed, there are no prospective studies that support the standard clinical teaching that a tight cervical cord is an indication for an awake intubation: medicolegal considerations are probably the main justification for this practice.

Acute Spinal Cord Injury

Although most victims of spinal cord injury are young, the physiologic consequences of the spinal injury and, in many cases, associated trauma make the acute management of these patients challenging. The cervical spinal cord is injured more commonly than thoracic or lumber areas and results in the greatest systemic physiologic disturbance. Furthermore, the presence of a cervical cord injury should lead one to suspect associated head, face, or tracheal trauma; thoracic and lumbar spine injuries are often associated with chest or intra-abdominal trauma. In any event, the main goal of initial management is to prevent secondary damage to the injured spinal cord by stabilizing the spine and correcting circulatory and ventilatory abnormalities that can exacerbate the primary injury.

Neck Stabilization and Airway Management

Immobilization of the neck in a neutral position is the overriding principle of care for patients with known or suspected cervical cord instability. Since 10% to 30% of traumatic spinal fractures are missed on initial evaluation and failure to immobilize the neck initially may increase the incidence of a secondary neurologic deficit sevenfold,[164] one must have a high index of suspicion despite a supposedly "cleared" cervical spine. Immobilization accomplished by having an assistant place his or her fingers on both mastoid processes and applying gentle in-line traction is superior to collars for management of cervical instability,[137] but may distract and sublux the fracture site if traction is too vigorous.[8] Methods of immobilization that splint both the head and torso to a rigid board and block lateral movement with sandbags at either side of the head decrease neck movement to about 5% of normal.[3] Soft and hard collars warn that a neck injury may be present, but probably do little to prevent movement of the neck during airway management because they permit approximately 75% to 95% of normal neck flexion and extension.[25, 91, 161]

The best approach to airway management in the patient with an unstable cervical spine is the subject of considerable, often emotional, controversy. A radiographic study using cadavers demonstrates that even basic airway maneuvers such as chin lift and jaw thrust seem to expand the disk space at the site of the injury and that anterior pressure on the trachea can cause posterior subluxation.[3] Direct laryngoscopy causes extension primarily at C1–2 in normal volunteers and some flexion in the lower cervical spine[88] that is reduced but not eliminated by manual in-line traction.[137] Nevertheless, provided the neck is stabilized, there is only anecdotal evidence that airway maneuvers actually endanger such patients, and large clinical experiences[30, 63, 147, 187] suggest that they do not. Because there is a high incidence of hypoxia among central nervous system trauma victims[117, 131, 176] but a relatively low incidence of cervical spine instability,[81] careful but expeditious airway management can be lifesaving. Both awake tracheal intubation and direct laryngoscopy with the aid of muscle relaxants in anesthetized patients seem to be safe and acceptable approaches.[30, 63, 81, 147, 165, 187] For example, the incidence of a change in neurologic status between initial examination and discharge in 136 cervical-spine–injured patients intubated awake was no different than that of 233 such patients who were not intubated.[147] Similarly, there is no evidence of neurologic deterioration following direct laryngoscopy in anesthetized patients provided the head and neck are stabilized, but clinical series are small.[63] The use of muscle relaxants in the presence of an unstable neck is also controversial because of concern that loss of the cervical muscle splinting may increase instability. Whether the neck muscles effectively splint an unstable spine has not been studied, but excellent results reported from intubation under general anesthesia using muscle relaxants on more than 3000 patients with suspected cervical spine injury suggest that neither the maintenance of muscle tone nor the anesthetic circumstances (asleep or awake) are materially important.[63] In fact, in a small recent retrospective review of 150 patients with traumatic cervical spine injuries, there was no difference in neurologic outcome related to whether patients were intubated awake or after induction of general anesthesia, and failure to immobilize the neck did not adversely affect outcome.[187] Much larger studies will be necessary to unequivocally settle whether one approach is safer than another, but in the meantime, perhaps the best approach is to stabilize the neck and intubate the trachea using the technique with which one is most expert.[30, 81, 165]

Spinal Shock

One of the circulatory abnormalities associated with acute severe cervical or thoracic spinal cord injury is spinal shock. Physiologically this condition is very similar to that of spinal anesthesia and results from loss of sympathetic activity below the level of the lesion (due in this case to functional transection of the spinal cord). The resulting vasodilation, hypotension, and, if the lesion involves the cardiac accelerator nerves (T1–4), bradycardia, bradyarrhythmias, and atrioventricular (AV) block may persist for days to weeks after the initial insult.[118] Unopposed vagal tone, occasionally severe enough to cause extreme bradycardia or even cardiac arrest during tracheal suctioning or laryngoscopy, can be attenuated by atropine (albeit sometimes at significantly higher doses than usual) or isoproterenol. The optimal treatment for hypotension is controversial; fluids and vasopressors both have proponents. Enlarged intravascular capacity due to dilatation of arterial and capacitance vessels can be offset by fluid or α-adrenergic agonists such as phenylephrine, although the latter may restore blood pressure at the expense of increased afterload and a reduction in cardiac output.[134] Inability of these patients to increase heart rate or contractility due to loss of sympathetic input to the heart may make vasopressors with inotropic properties (e.g., dopamine) preferable. Diagnosing hypovolemia is difficult because tachycardia and peripheral vasoconstriction do not occur with high cord lesions.[131] A pulmonary artery catheter may be helpful in this regard and may be particularly useful if the patient has associated injuries or surgery is required. The response of left ventricular filling pressures and cardiac output to incremental fluid challenges can be used to guide fluid therapy; if hypotension, oliguria, or a low mixed venous oxygen tension do not improve by elevating pulmonary wedge pressure, inotropic agents should be considered.

Finally, because the inotropic and chronotropic effects of the sympathetic nervous system are attenuated or lost, patients with high cord injury may be unusually sensitive to the myocardial depressant effects of anesthetics.[134] Simply reducing the anesthetic agent concentration may result in a dramatic reversal of cardiac depression and improved blood pressure.

Respiratory Impairment

A spinal cord injury at T7–8 or above produces respiratory impairment because abdominal and intercostal muscle strength is lost. Both vital capacity and forced expiratory volume in 1 second (FEV_1) are reduced; functional transection of the cord between C5 and C6 reduces vital capacity and FEV_1 to just 30% of predicted.[117] Consequently, the patient's ability to cough and handle secretions is impaired, which, in turn, places the patient at increased risk for infection and hypoxia. In fact, the leading cause of death in such patients is pneumonia.[41] Impaired oxygenation also occurs in many patients with high spinal cord lesions despite normal alveolar ventilation,[117] so supplemental oxygen should be provided routinely. Because the diaphragm is innervated by C3–5, lesions at or above this level obviously produce life-threatening respiratory failure.

Resuscitation of the Injured Spinal Cord

Traumatic spinal cord injury causes a decrease in local SCBF and loss of autoregulation, leading to ischemia and tissue hypoxia.[194] Superimposed on this background, systemic arterial hypoxemia and hypotension, common sequelae of spinal cord injury, are not well tolerated by injured neural tissue and may lead to further (so-called "secondary") damage. Hence, the first, and probably most effective step in resuscitating the injured spinal cord is to prevent secondary cord damage by recognizing and correcting systemic circulatory and respiratory abnormalities. In addition, many other physiologic and pharmacologic strategies have been employed in experimental models for resuscitation of the injured spinal cord, but only a few have been investigated thoroughly enough to warrant consideration.

Steroids. Steroids have long shown promise in the laboratory, but clinical efficacy was demonstrated only recently. Steroids improve SCBF, restore impulse transmission, normalize calcium metabolism, and enhance functional neurologic recovery following spinal cord trauma in animals.[16, 79, 87] Nevertheless, an initial double-blind trial of methylprednisolone in human spinal cord injury that randomized victims to either high (i.e., 1000 mg bolus followed by 1000 mg/d × 10 d) or standard dose (i.e., 100 mg bolus followed by 100 mg/d × 10 d) methylpredonisolone groups found no difference in neurologic recovery between these two treatments, but did not compare outcome with untreated controls.[15] Because subsequent experimental work suggested that as much as 30 mg/kg of methylpredonisolone (i.e., 2 g for 70-kg adult) might be necessary for a beneficial effect,[17] another randomized, double-blinded, and placebo-controlled trial was conducted.[14] Patients received either 30 mg/kg of methylpredonisolone as a bolus followed by an infusion at 5.4 $mg \cdot kg^{-1} \cdot h^{-1}$ for 23 hours, naloxone 5.4 mg/kg bolus plus an infusion at 4.0 $mg \cdot kg^{-1} \cdot h^{-1}$, or equivalent volumes of placebo. Some improvement in the recovery of both motor and sensory function was observed at 6 weeks and 6 months among those treated with methylpredonisolone within 8 hours of spinal cord injury, whereas naloxone had no beneficial effect. However, many patients showed no improvement and no patient recovered neurologic function completely. Indeed, even among those who benefited from treatment, neurologic recovery was modest, usually consisting of improved function in several spinal cord segments, and probably insufficient to improve overall functional status in most cases. Complications were few, probably because the duration of treatment was short. The mechanism of action is uncertain, but because the effective dose far exceeds that present physiologically, steroid inhibition of lipid peroxidation and hydrolysis at the site of injury rather than a receptor action has been proposed. This study[14] is important not only because it has resulted in widespread clinical use of high-dose methylprednisolone in acute spinal cord injury, but also because as the first large, well-designed clinical demonstration of improvement in human spinal cord injury, it offers promise that more dramatic recovery may someday be achieved pharmacologically.

Opiate Receptor Antagonists. These are another class of agents that has proven effective in some models of spinal cord injury. Based largely on the demonstration that naloxone improves systemic hypotension, SCBF, and neurologic recovery in an experimental model of spinal cord trauma,[51, 52] endogenous opiates were hypothesized to play a role in the evolution of secondary damage following traumatic neural injury. Subsequent research[54, 55, 109, 203] indicated that activation of the κ-, but not the μ-subtype of opiate receptor was involved. Increased immunoreactivity at the injury site of the κ-agonist dynorphin[54] and enhanced κ-receptor binding[109] and the fact that the κ-receptor antagonist nalmefene improves neurologic recovery[55, 203] support this view. However, recent laboratory[10, 11, 76, 86] and clinical studies of spinal cord trauma[14, 57] fail to document a beneficial effect of naloxone in dosages so massive that it is no longer a selective μ-subtype opiate receptor antagonist. For example, in the aforementioned double-blind, randomized, controlled clinical trial of acute spinal cord injury,[14] treatment with naloxone, 5.4 mg/kg intravenously as a bolus, followed by 4 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ resulted in no better neurologic outcome than placebo.

Plasma Glucose. Numerous experimental and clinical studies indicate that a high plasma glucose concentration adversely influences recovery from ischemic neurologic injury.[44, 119, 132, 167] Because ischemia and extreme hypoperfusion are prominent features of the traumatized spinal cord,[194] it is reasonable to be concerned about hyperglycemia in this setting as well. Although the mechanism for the deleterious effect of hyperglycemia is not entirely clear, one theory[140] is that, in ischemic areas, tissue acidosis from anaerobic metabolism of glucose to lactate is worsened by hyperglycemia, triggering biochemical events such as an increase in intracellular Ca^{2+} and breakdown of cell membranes that ultimately lead to neuronal death. In the case of spinal cord ischemia, plasma glucose concentrations as little as 40 mg/dL above normal may profoundly worsen the injury.[44] There is even evidence that hypoglycemia is preferable to normoglycemia with respect to neurologic outcome from spinal cord ischemia.[167] However, concern about the deleterious effects of hyperglycemia must be tempered with the realization that the threshold concentration of plasma glucose that exacerbates injury varies considerably among studies and that hypoglycemia is difficult to detect and, therefore, potentially dangerous in anesthetized patients. Thus, it seems prudent to use glucose-containing intravenous solutions judiciously or not at all in victims of spinal cord trauma, but aggressive efforts to maintain a normal plasma glucose should await documentation of an adverse effect of glucose on the traumatized cord.

Hypothermia. Profound hypothermia is a classical measure to improve tolerance of the spinal cord and brain to ischemia, but the associated risks of marked cardiovascular and respiratory depression, arrhythmias, and tissue hypoperfusion limit its use largely to cardiac surgery. There is some evidence that profound regional hypothermia or moderate systemic cooling may benefit a traumatized spinal cord, however. Regional cooling of the spinal cord by irrigating locally with cold perfusate (3–5°C) through a posterior laminectomy has been used in spinal cord trauma victims with some success,[2] but never became popular perhaps because the improvement is transient and it is rarely possible to begin treatment within the 4 to 6 hours postinjury window during which it may be helpful. On the other hand, reducing rectal temperature 3°C (i.e., to 34°C) is easy to accomplish and may be beneficial[7, 20, 21]; it prolongs the duration of ischemia rabbit spinal cord can tolerate without a permanent deficit.[197] Hypothermia may act by mechanisms such as metabolic depression or reducing accumulation of neurotoxic excitatory neurotransmitters in damaged neural tissue.[21]

Anesthetics. The possibility that anesthetic may protect the injured spinal cord is a logical extension of work pertaining to ischemic or traumatized brain, but only a few experimental and no clinical studies concern this topic. Some electrophysiologic, histologic, and outcome studies suggest that barbiturates enhance tolerance of the spinal cord to ischemia[154, 155] and compression[166] and trauma,[48] but results are not uniform[98, 170] perhaps because of the dosage or timing of barbiturate administration (i.e., before or after the injury) differ. Halothane, the only inhalational anesthetic studied thus far, improves neurologic recovery following a contusion injury of the spinal cord relative to pentobarbital or nitrous oxide anesthesia[170] and enhances tolerance to compression and ischemic injury.[27] However, it may be that virtually all anesthetics are beneficial in this situation; halothane, nitrous oxide-fentanyl, and subarachnoid lidocaine all extend the duration of spinal cord ischemia and compression that can be tolerated without injury.[27] Indeed, despite the putative role of endogenous opiates in the pathophysiology of spinal cord injury, there is no justification for concern that narcotic anesthesia might have a harmful effect on the injured spinal cord.[26]

Other Investigational Agents. Influx of Ca^{2+} into cells appears to contribute to the development of secondary neuronal damage after ischemic or traumatic injury of the central nervous system.[151] Accordingly, calcium channel antagonists have been investigated in spinal cord injury, albeit with rather disappointing results. Nimodipine improves SCBF immediately after compression injury only if blood pressure is maintained by vasopressors,[73, 75] but fails to improve SCBF and neurologic outcome 24 to 96 hours later.[53, 85] Nicardipine also fails to improve functional and histologic recovery 4 weeks after traumatic spinal injury.[9] Other presumed mediators of secondary injury include free radicals, which are hyperreactive ions produced in ischemic or injured tissues by degenerative reactions, including formation of free fatty acids from cell membranes. The free radical scavenger superoxide dismutase reduces the incidence of aortic occlusion-induced paraplegia when given intrathecally,[1] but is ineffective systemically.[98, 192] Pretreatment with the scavenger vitamin E plus selenium improves SCBF after traumatic injury,[79] but its effect on neurologic outcome is unknown. Endogenous excitatory amino acid neurotransmitters such as glutamate and aspartate also appear to produce neurotoxicity,[82] possibly by receptor-mediated mechanisms. Hence, MK-801, an antagonist of the *N*-methyl-D-aspartate receptor subtype, has been studied in models of spinal cord trauma[56] and ischemia[103, 203] and seems to improve neurologic and histologic outcome. Like all new treatment strategies, the role of these agents in the future of spinal cord resuscitation is uncertain.

A unique approach to spinal cord resuscitation for which there is actually some clinical experience involves administration of GM_1 ganglioside, a complex acidic glycolipid compound present in neuronal membranes. This agent is thought to act by becoming incorporated into neural membranes damaged by trauma.[50] A recent prospective, randomized, placebo-controlled trial of GM_1 ganglioside in 34 patients with spinal cord injury demonstrated a modest improvement in muscle strength and overall neurologic function.[59] However, the small size of the study plus the fact that, despite randomization, there was some maldistribution of patients (i.e., the treatment group had more severe deficits) will require other studies with this promising drug before its clinical utility is clear.[198]

Surgery for Correction of Scoliosis

General Considerations

Scoliosis is manifest as a lateral curvature of the spine and accompanying rotation of the vertebrae, resulting in distortion of the rib cage. These anatomic deformities are important when spinal or epidural anesthesia is considered for nonspine surgery, but also have implications for respiratory and cardiovascular function. Lung volumes including vital capacity and compliance of the respiratory system are reduced, with the magnitude of the decrease related to the angle of curvature.[93] Ventilation-perfusion mismatching due to underventilation of lung regions compressed by the rib cage deformity causes hypoxemia that, combined with impaired development of vascular beds in these lung regions, eventually leads to pulmonary hypertension and right ventricular hypertrophy.[93] Rapid shallow breathing develops because of the restrictive nature of the disease, but Pa_{CO_2} is normal initially despite an increased dead-space-to-tidal-volume ratio.[93] Hypercapnia may occur as the pulmonary disease worsens or neuromuscular disease is superimposed.

With respect to the spinal cord, surgical procedures to correct scoliosis are associated with a significant risk of intraoperative spinal cord injury. A survey in 1975[133] showed a 0.72% incidence of acute neurologic complications and approximately 50% of these involved complete paraplegia. More recently, a 2.8% to 4%[58, 200] incidence of major postoperative neurologic complications has been reported, perhaps because the use of segmental spinal instrumentation allows more drastic correction of spine curvature. Perioperative spinal cord ischemia is the presumed mechanism of injury. Distraction of the spine in animals to the point that SSEPs are altered reduces local SCBF by more than 50% and further distraction to the point that SSEPs are totally abolished produces almost complete ischemia of the spinal cord at or near the site.[43] Perhaps for this reason, SSEPs are sometimes used during scoliosis surgery as an electrophysiologic index of spinal hypoperfusion (see previous discussion). Furthermore, the practice of deliberately reducing blood pressure in an effort to control blood loss could also compromise SCBF and predispose to spinal cord dysfunction.

Controlled Hypotension

Reducing MAP to 60 mm Hg during spine surgery in normotensive patients is believed to decrease blood loss and transfusion requirements and improve operating conditions, but does not reduce operating time.[72, 138, 144] While studies indicate that SCBF is well maintained in normal animals when hypotension is produced pharmacologically, it is not known whether autoregulation functions normally in patients with scoliosis. Published clinical experiences are small; for instance, in an uncontrolled study of 24 patients undergoing Harrington rod instrumentation under sodium nitroprusside–induced hypotensive anesthesia, five had alterations in SSEPs during spine straightening that resolved when hypotension and hemodilution were reversed.[72] Although none of the patients had a neurologic deficit, the series is too small to draw meaningful conclusions with respect to the role of hypotension in neurologic deterioration. The agent used to provide hypotension may have a bearing on the subject because each affects SCBF differently. For instance, SCBF decreases initially in dogs when MAP is reduced by 50% using sodium nitroprusside, but returns to baseline 30 minutes later, presumably because autoregulation is restored.[100] SCBF is maintained when nitroglycerin is used to reduce MAP to 50 to 55 mm Hg,[184, 185] but decreases in proportion to MAP when trimethaphan is the hypotensive agent.[101] Using deep inhalational anesthesia to produce hypotension is not always practical for this type of surgery because it hinders execution of the wake-up test and interferes with evoked potentials monitoring, not to mention that its effects on SCBF are unknown. Another effort to reduce the requirement for blood transfusion involves combining hemodilution with controlled hypotension. Here again, at the same hematocrit and MAP, SCBF and oxygen supply vary with the hypotensive agent; sodium nitroprusside maintains adequate SCBF and oxygen supply, whereas adenosine may not.[35, 36] Despite such experimental evidence, however, it is impossible to say whether hypotensive anesthesia or a specific hypotensive agent influences the probability of spinal cord ischemia during scoliosis surgery.

Surgery of the Thoracoabdominal Aorta

Thoracoabdominal aortic surgery is unique because spinal cord damage can occur even though the spine is not the target of the surgery. These procedures are associated with a substantial risk of paraplegia (0.1% in coarctation repair to 24% for emergency resection of dissecting thoracic aneurysms[168, 193]) that varies with the adequacy of collateral flow, location and extent of the surgical lesion, and urgency of treatment. The great radicular artery of Adamkiewicz is of particular importance because it is a source of flow to a large portion of the spinal cord and usually arises from the aorta between T8 and L3.[168] Another less obvious problem with aortic cross-clamping is that it increases CSFP in animals and in some patients.[6, 80, 108, 143] Consequently, SCPP can be reduced to dangerous levels by cross-clamp–induced distal hypotension and increased CSFP (SCPP = mean aortic pressure − CSFP in this case). The etiology of the increase in CSFP is unclear. One theory[160] claims that hypertension occurring proximal to the aortic cross-clamp exceeds the limits of cerebral autoregulation and increases cerebral and spinal CSFP. However, because control of arterial blood pressure does not seem to reduce CSFP,[29, 37, 96, 111–114, 148, 160, 188, 189] other mechanisms not yet identified must also be involved.

Strategies to reduce the incidence of spinal neurologic dysfunction during thoracoabdominal aortic surgery address the general problem of spinal cord hypoperfusion and range from efforts to identify patients at most risk to administration of putatively protective agents directly into the subarachnoid space. Preoperative angiography is rarely helpful to identify critical radicular branches of the aorta.[29] Intraoperative SSEP monitoring has been used to identify individuals with poor collateral flow or to assess adequacy of efforts to perfuse the distal aorta.[37, 111, 112, 114, 148] For instance, SSEP studies during thoracoabdominal aortic surgery reveal a high incidence (about 20%–70%) of reversible spinal ischemia (i.e., recoverable loss of the SSEP without complete spinal cord dysfunction)[37, 95, 96, 111–114, 148] and an extremely variable time (5–40 minutes) to loss of the SSEP after cross-clamping,[37, 95, 114] which probably reflects considerable (patient-to-patient) variability in collateral flow. The duration of SSEP loss that can be tolerated without permanent neurologic injury also varies, so failure of SSEP conduction cannot be used to predict how much longer a given patient could tolerate ongoing spinal cord ischemia. In addition, distal hypotension affects conduction in the peripheral nerves from which SSEPs are generated and may interfere with SSEP monitoring by producing changes similar to those from spinal ischemia. Simultaneous recording of SSEPs generated by posterior tibial nerve stimulation and spinal cord stimulation with an epidural electrode revealed that loss of posterior tibial SSEPs with retained spinal cord SSEPs always resulted in normal postoperative neurologic outcome.[153] Concern about motor tract function has recently led to experimental[115, 150] and clinical studies[153] of MEP monitoring to this type of surgery, with promising initial results.

One direct approach to reduce the incidence of neurologic complications during aortic surgery is to attempt to improve distal perfusion using vascular bypass procedures or shunts. Some workers[37, 95, 111] claim that maintaining distal aortic pressure above 60 mm Hg with some form of bypass or shunt if necessary is beneficial, while others assert that shunting or bypass are unnecessary,[39, 127] harmful,[28] or ineffective,[190] because they are too small,[149] distal,[192] or fail to augment flow to the thoracic spinal cord.[190] Another way to improve SCPP and potentially positively influence neurologic outcome is to attenuate or prevent an increase in CSFP with either osmotic diuretics or withdrawal of CSF through a lumbar subarachnoid catheter. Both techniques increase SCBF and are effective in reducing the incidence of paraplegia associated with occlusion of the thoracic aorta in most animal studies.[12, 143] Drainage of CSF in particular is promising and has become popular recently, but a few reports dispute efficacy in animals,[12, 150, 192] and clinical studies are either too small to confirm a benefit[143] or lack an appropriate (i.e., concurrent rather than historical) control group.[202]

Few other physiologic and pharmacologic strategies to improve spinal tolerance have been used clinically for cross-clamp–associated ischemia. One mode of protection unique to this situation involves intrathecal administration of a putatively protective agent. Intrathecal papaverine, selected because it improves SCBF in the thoracic cord of primates during aortic occlusion,[192] is the only agent for which a small clinical experience exists. In a very small study (only 11 patients in the papaverine group) the incidence of paraparesis or paraplegia was reduced from 42% in patients treated with conventional methods (i.e., no CSF drainage or papaverine) to 9% in those treated with CSF drainage and papaverine before aortic cross-clamping.[188, 189, 191] More recently, intrathecal tetracaine has been reported to reduce the incidence of neurologic dysfunction after aortic occlusion in rabbits.[18] While its mechanism of action is unclear, it may involve inhibition of ion fluxes (i.e., a membrane-stabilizing effect) or metabolic or blood flow effects (see previous discussion). Care must be exercised before drugs are administered intrathecally for the purposes of protection, however, because few have undergone thorough preclinical testing and clinical experience with this approach is extremely limited.

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CEREBRAL PROTECTION, RESUSCITATION, AND MONITORING: A LOOK INTO THE FUTURE OF NEUROANESTHESIA

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NEW DEVELOPMENTS IN THE TREATMENT OF SUBARACHNOID HEMORRHAGE

Implications for Anesthetic Management

Marc A. Pilato, MD

In North America 28,000 people suffer from subarachnoid hemorrhage (SAH) each year. Approximately 10,000 die from the initial insult, and another 8000 die or are permanently disabled secondary to the initial bleed and its sequelae. The most feared consequences of SAH are rebleeding and vasospasm. During the last 10 years, there has been improvement in the perioperative management of SAH and prevention of the sequelae of the disease. Timing of surgery to prevent rebleeding of the SAH was controversial, but only early operation effectively prevents rebleeding. Vasospasm occurs in patients with early operation, but the treatment of vasospasm has improved with prophylactic calcium channel blockers. In patients who develop vasospasm, the use of hypervolemic, hypertensive, hemodilution therapy is effective. It remains to be seen whether the overall management morbidity and mortality of the disease has improved.

NATURAL HISTORY AND PATHOPHYSIOLOGY

Cerebral aneurysm and SAH are common problems in North America. Approximately 400,000 people have unruptured aneurysms. In some studies, 4% to 6% of patients at autopsy have unruptured aneurysms. It has been estimated that one out of five aneurysms rupture. One half to one third of

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ruptures never cause any symptoms.[89] For unruptured aneurysms, the rate of spontaneous hemorrhage is approximately 1% per year.[45] The incidence of SAH varies according to the population studied. In the United States, the death rate from SAH ranges from 12 to 16 per 100,000.[26, 48]

The pathogenesis of cerebral aneurysm is still unknown. Evidence points to congenital weakness in the muscular layer of the vessel wall, whereas other data suggest that degenerative changes in the wall causes aneurysm formation. Cerebral vessels may be more prone to aneurysm formation than extracerebral vessels. Cerebral vessels differ from extracerebral vascular tissue: they lack perivascular support and have thin layered walls. There are three tissue layers in the vascular wall of the cerebral arteries: the intima, muscular media, and outer adventitia, which has a collagenous layer. Cerebral vessels do not have the external elastic media that systemic arteries possess. The muscular media and the adventitial layer are also thinner than extracerebral vessels. Because of the lack of perivascular support and thinner vascular walls, the cerebral vessels are prone to aneurysm formation, especially at branch points in cerebral vasculature where the arteries are subjected to repeated hemodynamic stress.

There are several syndromes that are associated with aneurysm formation: coarctation of the aorta, fibromuscular dysplasia, and polycystic kidneys.[23] In one study of patients with SAH, the collagen in the adventitial layer was defective in structure. These patients had deficient formation of type III collagen. This defective collagen compromised the ability of the vessel wall to withstand the normal circulatory stresses and contributed to the formation of the aneurysm. Type III collagen deficiency is also found in Ehlers-Danlos syndrome type IV, and there are several case reports of SAH in these patients.[59, 62]

Although genetic predisposition plays a role in the formation of aneurysms, there are other factors that have been shown to contribute to the risk of aneurysm formation. Hypertensive patients appear to be at risk compared with normotensive patients. Hypertension may be instrumental in the development of an aneurysm and also in the rupture of the aneurysm. Hypertension is not associated with increased risk of rupture, but in patients with a previous hemorrhage, systolic blood pressures greater than 170 have been shown to be related to an increased risk of rerupture.[62]

The incidence of aneurysms increases with increasing age, but old age itself does not seem to be a risk factor for rupture of the aneurysm. The peak age for rupture is between 55 and 60 years of age in the United States. Women have an increased risk of aneurysm formation, which might explain their preponderance in epidemiologic studies of SAH. However, there does not seem to be an increased risk for rupture for women.[62]

Size and location of the aneurysms are important factors in determining the risk of rupture. Most aneurysms originate at bifurcations of major conducting arteries in the cerebral circulation. These areas are subject to repeated hemodynamic stresses, in regions where the tunica media and elastica are absent. Eighty percent to 85% of the aneurysms are in the anterior circulation. The most common locations are (1) the internal carotid artery, usually at the posterior communicating artery, (2) the anterior cerebral artery, most commonly at the anterior communicating artery, and (3) the middle cerebral artery. When the posterior circulation is affected, the most common site is the basilar termination.[89] Small aneurysms are less than 15 mm in diameter, large lesions are 15 to 25 mm in diameter, and giant aneurysms are greater than 25 mm.[23] The critical size for rupture is smaller than first thought. Four to 7 mm seems to be the critical diameter for rupture. Small aneurysms are as dangerous as are larger ones.[13]

Rupture of the aneurysm can be minor or catastrophic, depending on the location and duration of the bleed. Fifteen percent to 20% of patients with SAH never survive the initial bleed to reach medical attention.[51, 62] Most often (in 75% of cases) the symptoms and signs are minor. The classic sign is the "sentinel headache," a headache that is characterized by the patient as unlike anything that they have ever experienced before. If a careful history is taken, this is found in almost one quarter of the patients with SAH (one retrospective study found this symptom in 70% of patients with a major bleed)[39] and precedes a major bleed by about 2 weeks.[61] Other symptoms are nausea, vomiting, and occasionally a loss of consciousness. These symptoms are seen in 60% of patients with SAH. If the bleeding is not stopped either by formation of a clot or tissue pressure, then coma and death can ensue. Mortality from the first SAH is staggering: 50% of patients die as a result of this first hemorrhage.[13, 26, 51]

Survivors of the first hemorrhage face three threats: 25% to 30% will not recover, secondary to the effects of the first hemorrhage; 9% to 22% will have a rebleed during the first 2 weeks after the hemorrhage; and 11% to 34% will have delayed neurologic deficits with permanent disability and death.[40] The delayed complications of SAH are devastating: recurrent bleeding, vasospasm, and acute hydrocephalus.

Blood in the subarachnoid space has many consequences. Increased intracranial pressure (ICP) can result, with or without communicating hydrocephalus. The raised ICP can also result from resistance to cerebrospinal fluid (CSF) outflow, cerebral edema secondary to tissue damage, or a combination of these.[15, 18, 23, 83]

Neurologic deficits are common after SAH; they could be secondary to the hemorrhage itself, a result of the raised ICP, another bleed of the aneurysm, or from cerebral ischemia.

There is a very high rate of rebleeding in SAH patients. The peak time for rebleeding is during the first 24 hours after the initial bleed, not 7 days later as was previously thought. Fifty percent of patients with SAH rebleed within the first 24 hours, and the rate decreases to 30% at 15 days, 5% at 40 to 90 days, and 3% at 6 months.[45] Rebleeding is more catastrophic than the initial bleed. The presence of subarachnoid clot from the first SAH forces the blood from a rerupture into the brain parenchyma or into the ventricular system, giving rise to a fatal or life-threatening hematoma. Rebleeding in the first week is never confined to the subarachnoid space.[45, 82]

Cerebrovascular vasospasm is another feared and frequent complication of SAH. It occurs in 20% to 40% of all patients with SAH. It has an adverse effect on the outcome after SAH. The likelihood of good recovery is reduced by approximately 50% and the mortality doubles. It is now the leading cause of death after SAH: 7% die and another 7% are disabled by vasospasm. The computed tomographic (CT) scan on admission to the hospital is the best predictive indicator for vasospasm.[3–5, 13, 31, 32, 42, 46, 48, 51, 82, 85]

The pathogenesis of vasospasm is poorly understood. There are no causative agents known, and the reason for arterial narrowing seen during angiography is unknown. Because there is no satisfactory animal model of vasospasm after SAH, research has been hampered. The major hypotheses of the cause of vasospasm are contraction of cerebral arterial smooth muscle secondary to vasoactive substances in the CSF or impairment of vasodilatory activities (a prostacyclin:thromboxane imbalance), presence of oxyhemoglobin in the CSF, a proliferative vasculopathy, an immune process, an inflammatory process, or a mechanical phenomenon.[46]

What is known is that blood in the subarachnoid space is crucial to the development of the syndrome. There is a 3-day lag from the initial bleed till the clinical syndrome is evident. The clinical syndrome of vasospasm is to be differentiated from the angiographic arterial narrowing seen during cerebral angiography. Although 70% of patients develop arterial narrowing seen during angiography, only 20% to 40% develop clinical neurologic deficits. Clinical vasospasm is characterized by impaired orientation and a decreased level of consciousness followed by focal deficits. Arterial narrowing seen by angiography seems to be a structural and pathologic change in the arterial wall as opposed to a physiologic change, which occurs after contraction of smooth muscle in the vascular wall.

The clinical diagnosis of vasospasm is based on the time of onset (4–9 days post-SAH, peaking on day 7), the rate of development (hours), the nature of the deficits, and the exclusion of other causes (rebleeding, increased ICP, metabolic disturbances, and so forth).

CLINICAL PRESENTATION

The most frequent presentation of a patient with an intracranial aneurysm is the sentinel headache. Other symptoms of SAH such as nausea, vomiting, neck pain, back pain, photophobia, and loss of consciousness are also seen. Neurologic signs that accompany these symptoms include acute confusion, memory deficits, aphasia, hemiparesis, third nerve palsy, sixth nerve palsy, and so forth. A high index of suspicion is extremely important for the admitting physician, because not every patient with SAH appears gravely ill. As Drake said, "The major problem will be to educate the public, as the 'warning leak' is not always suddenly vicious and frightening head pain but frequently is a vague and generalized headache or even just a sore, stiff neck."[26] It is estimated that 25% of patients with SAH are treated for other diseases.[4]

Patients with SAH are assessed clinically using the Hunt and Hess clinical scale.[44] It is a modification of the Botterell classification. It was developed to evaluate the risk of surgery based on the neurologic status of the patient on admission to the hospital. The grading system is presented in Table 1.

The overall outcome for a patient depends on the volume, location, and rate of bleeding, age of the patient, and underlying medical disease. In general, the poorer the grade on admission to the hospital, the worse the prognosis.

PREOPERATIVE DIAGNOSIS

In the past, blood in the CSF from a lumbar tap would make one highly suspicious of an SAH. Today, CT has become the diagnostic tool for SAH. The

Table 1. RISK OF SURGERY BASED ON NEUROLOGIC STATUS

Grade	Neurologic Status
I	Asymptomatic, or minimal headache and slight nuchal rigidity
II	Moderate-to-severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
III	Drowsiness and confusion or mild focal deficit
IV	Stupor, moderate-to-severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund appearance

CT is able to distinguish the location and distribution of blood in the basal cisterns, or if there has been a bleed into the parenchyma of the brain. The CT scan is important for predicting the probability of complications from SAH: infarction, intracerebral bleeds, and hydrocephalus.[5, 18, 32, 42, 82] It is now well known that vasospasm and hydrocephalus have a high degree of correlation to the amount of blood seen by CT scan.

Angiography is used to determine the location of the aneurysm. Four-vessel angiography is used to find if there are multiple aneurysms, which occur in 15% of patients with SAH.

SURGICAL MANAGEMENT

Surgical management of SAH before 1980 included a waiting period of 10 or more days after the initial hemorrhage before the definitive operation. There were several reasons for this waiting period. Early operations on patients with fresh SAH were difficult for neurosurgeons because the brain after SAH was edematous and covered with subarachnoid clot. The therapy used in this situation was crude and often ineffective. Knowledge of cerebral hemodynamics and ICP was rudimentary at best.

Another complication of early surgery was vasospasm. It occurred commonly during the postoperative course, claiming many patients who had a perfect operation. Vasospasm was known to occur from 3 days after the initial hemorrhage until 10 to 14 days after the initial SAH. As a result, surgeons were unwilling to operate on a patient with a fresh SAH; surgery was delayed until the threat of vasospasm had subsided.

Surgeons waited so that the brain could recover from the effects of the hemorrhage and the patient's neurologic condition could be stabilized. This waiting period produced excellent operative results for the patients who had survived to come to the operating room. Unfortunately, the waiting period was associated with significant morbidity and mortality from rebleeding, vasospasm, and the effects of the initial hemorrhage.

It was thought that the peak time of rebleeding was on day 7 post-SAH. This theory was not supported by later clinical studies.[13, 45, 47] To prevent rebleeding while waiting for the operation, antifibrinolytic agents such as aminocaproic acid and tranexamic acid were used. These drugs did reduce the risk of rebleeding, but not completely. The drugs were not effective until 3 days after the start of therapy. This was a problem because the highest rate of rebleeding is the first day after SAH. The antifibrinolytic drugs did reduce the morbidity and mortality secondary to rebleeding, but at a price. There was a higher incidence of vasospasm and cerebral infarction in those patients. Antifibrinolytic drugs did not reduce overall morbidity and mortality in patients with SAH.

During this time, there was rapid progress in the surgical approach to the disease. Operative microscopes were developed, which enabled the surgeon to operate and dissect with accuracy and gentleness. Surgical clips were developed to temporarily occlude vessels or that could be placed permanently across the neck of an aneurysm to occlude it.[26, 27] Neuroanesthesia advanced along with surgery. Anesthesiologists learned how to manipulate hemodynamics, safely inducing hypotension, to provide cerebral protection first through hypothermia, and then with barbiturates. ICP was controlled through the use of anesthetic agents, hyperventilation, and diuretics to provide surgeons with a slack operating field.[36, 55] Operative morbidity and mortality was reduced. Since 1980, mortality in the surgical management of SAH was less than 3%.[34]

The concept of overall management morbidity and mortality was developed, because although the surgical results were impressive, the likelihood of someone surviving an initial SAH was still only 50%. Additionally, many neurosurgeons were not satisfied with the low percentage of patients not only surviving, but also returning to a normal, functional level. A more aggressive mode of therapy was needed to salvage patients.[67]

Faced with the problem of high management morbidity and mortality, neurosurgeons in Japan decided to treat patients as early as possible after SAH. They tried to operate within 48 hours of the hemorrhage. They aggressively removed clots from the surface of the brain. They used techniques involving temporary clipping and cerebral protective agents.[78, 79] Their results encouraged others to perform similar operations. Even so, many surgeons in North America were unconvinced that early operation improved mortality and morbidity.[21, 27] A large multicenter study was performed to find if there was any difference in morbidity and mortality in early versus late operation for SAH.[48, 49]

The Cooperative Aneurysm Study found that the leading causes of death and disability in SAH patients were vasospasm, the direct effect of the initial insult, rebleeding, and surgical complications. The mortality from rebleeding and vasospasm was equivalent, but the morbidity from vasospasm accounted for 39% of the cases of disability. The direct effect of the initial SAH was implicated in 22% of patients with morbidity and surgical complications in 14% of patients with morbidity.

The conclusion was patients who had early operations had results at least equal to patients who had delayed surgery. Good-grade patients (Hunt and Hess grade I or II) did well despite the timing of the surgery. There was a tradeoff: the risk of performing early surgery, with its high risk of postoperative complications, was offset by the risk of preoperative complications in the late surgery group. However, it was stated that if a method was found to prevent vasospasm in the postoperative period, then the results of early operation could be much improved because rebleeding was prevented.[48, 49]

Therefore, the prevention of vasospasm and the reduction of surgical complications became the focus of research in the last decade. The prevention of vasospasm is based on the use of calcium channel blocking agents. Calcium channel blocking agents are similar to the agents used for dilatation of vascular arteries in the treatment of hypertension or coronary artery spasm. However, these agents, nimodipine and nicardipine, have been shown to have selective vasodilatory action on the cerebral vasculature. These agents have also been shown to prevent cerebral vasospasm after SAH.[6, 11] The combination of early surgery to prevent rebleeding with the perioperative use of nimodipine to decrease vasospasm has improved surgical outcome. The incidence of clinical vasospasm, which occurs in approximately 30% of patients operated on (untreated historical controls), was reduced in some studies to 2%.[40]

The mode of action of calcium channel blockers in preventing vasospasm is still unknown. Patients still exhibit arterial narrowing during angiography, but the incidence of postoperative neurologic deficit is decreased with the use of nimodipine. It is not effective in reducing angiographic spasm. It has been shown to dilate pial arteries under direct observation.[12] An alternative explanation is a cerebral protective effect of nimodipine preventing a catastrophic increase in intracellular calcium, which can accompany ischemia.[6, 11, 33, 34, 40, 55, 60, 63, 65, 66, 69, 77]

Vasospasm sometimes occurs in patients with calcium channel blocker therapy. Therapy for symptomatic vasospasm developed after an understanding of cerebral perfusion pressures and autoregulation in the injured brain was appreciated. Autoregulation of cerebral blood flow is impaired in regions with vasospasm.[30, 85] In these areas, cerebral blood flow is dependent on perfusion pressure. Increased flow to the affected area means increasing the blood pressure, volume loading the patient, and hemodiluting the patient to a hematocrit of 30% to 35% to optimize the rheologic properties of blood.

There are hazards to this type of therapy: ICP can increase secondary to the increased blood flow, leading to a paradoxical decrease in cerebral perfusion pressure and a worsening of ischemic edema. Unruptured aneurysms are also at risk, preventing the use of this therapy in nonoperative patients. Patients who have a history of cardiovascular disease can develop myocardial ischemia or congestive heart failure with this type of therapy. Invasive hemodynamic monitoring with an indwelling arterial line and Swan Ganz catheter is necessary in this class of patient.[14]

In patients who had clinical vasospasm and were treated with hypertensive, hypervolemic hemodilution therapy, decreasing pulmonary wedge pressures correlated with neurologic deficits. Frequent monitoring and prompt correction of inadequate filling pressures improved, and in most cases eliminated neurologic deficits, and was the best method of preventing neurologic deficits.[31]

Another development in the surgical management of SAH was the aggressive treatment of poorer grade patients (Hunt and Hess grade III and IV). After the admission CT scan was performed, it was evaluated for brain damage secondary to the initial hemorrhage. Patients with no damage had ventriculostomies inserted if they had increased ICP. Patients with ventriculostomies frequently improved their grade. These patients were operated on within 24 hours. Patients with severe brain damage, who were not operated on, did not survive. It was thought that raised ICP produced a decrease in cerebral perfusion pressure; this caused patients to appear worse on admission. When the increased ICP was relieved and the cerebral hemodynamics improved, the clinical grade improved.[15, 34]

As surgical therapy for SAH evolved, monitoring of cerebral function also advanced, giving a better understanding of the therapeutic maneuvers that were attempted and providing guidance as to the clinical efficacy of these maneuvers. Measurement of cerebral blood flow moved from the laboratory to the bedside, with profound implications for the treatment of SAH. Using xenon-133 tracer techniques and regional blood flow measurement, patients with SAH had impairment of autoregulation and response to CO_2. Better-grade patients had less impairment than patients who were Hunt and Hess grade III and IV, and they returned to baseline reactivity sooner than those patients.[85] The degree of vasospasm exhibited by patients after SAH correlated with the degree of impairment of autoregulation. Focal impairment of autoregulation occurred during periods of hypotension in patients who had little or no spasm as evidenced by arteriogram, and who had normal or slightly reduced regional cerebral blood flow during resting state studies.[84] These studies have implications for the production of intraoperative cerebral ischemia when induced hypotension is used to prevent the rupture of aneurysms. Decreased cerebral blood flow was observed in several patients who developed delayed ischemic deficits postoperatively. However, there were no correlations of decreased cerebral blood flow with associated neurologic deficits.[30, 64] Patients with impaired autoregulation are susceptible to cerebral ischemia when exposed to systemic hypotension, an increase in ICP, or increased pressure on tissue at risk, i.e., retraction of the brain in the approach to the aneurysm.[43]

The measurement of CBF with the radioactive tracer technique is cumbersome and provides only a periodic measurement of the dynamic phenomenon of vasospasm. The need for a noninvasive continuous method of monitoring

CBF was met by the neurophysiologist Rune Aaslid and his development of the transcranial Doppler (TCD).[2] With this instrument, it became possible to noninvasively measure changes in cerebral blood flow velocity in the large conducting arteries at the base of the brain. If one assumed that the diameter of the conducting arteries remained constant, then the change in blood flow velocity correlates with change in cerebral blood flow. These changes in the flow velocities were thought to reflect changes in the resistance vessels downstream from the conducting vessels. Flow velocities in the middle cerebral artery were increased in patients who had vasospasm, and there was correlation in the amount of increase in flow velocity and the amount of vasospasm.[1, 70] Increased flow velocities were measured by the TCD before angiography showed narrowing of the arteries, and early and steep increases of the flow velocity were seen in patients who would go on to develop delayed ischemic deficits.

The TCD is useful in the diagnosis of vasospasm and can be used to anticipate the development of delayed ischemic dysfunction and institute treatment for the ischemic syndrome.[70, 71] The TCD is also used to determine whether prophylactic calcium channel blocker therapy is effective and if therapy with hypervolemic, hypertensive, hemodilution improves cerebral blood flow.[34, 40, 66]

Although cerebral blood flow studies and TCD provide information about the perfusion of the brain, neither of these modalities provide information about the functioning of the brain or neural pathways. The TCD and the collimeters for cerebral blood flow measurement in their present configurations are impractical for intraoperative monitoring. Intraoperative monitoring is necessary because many of the maneuvers during aneurysm surgery place the brain at risk for global or focal ischemia: induced hypotension, brain retraction, temporary clipping, and closure of terminal arteries.[28] The use of somatosensory-evoked potentials (SSEPs) during aneurysm surgery provides a way of detecting compromised cerebral perfusion in real time, enabling the surgeon to alter his or her approach and improve a potentially harmful situation. SSEPs provide a sensitive monitor of decreased perfusion. Friedman states: "The warning provided by the evoked potential changes afford the surgeon the opportunity to intervene before irreversible damage occurs."[35]

Central conduction times were changed in patients who had temporary clipping of major conducting arteries, and prolongation of conduction times occurred in a majority of patients. Intraoperative abnormalities of the conduction times correlate well with postoperative neurologic status of the patients. However, prolongation of the conduction time does not always correlate with the final outcome of the patients.[50, 80]

To produce useful and timely information rigorous techniques must be used in recording SSEPs. The evoked potential pertaining to the area at risk must be monitored. For the internal carotid artery, the median nerve SSEP is necessary. For the anterior cerebral artery or anterior communicating artery territory the posterior tibial SSEP must be monitored. For aneurysms in the basilar system, SSEP have not always proved a sensitive monitor, and it might be necessary to use motor-evoked potentials. Only sensory or motor pathways can be monitored with the present technology. Other types of deficits of course are missed by these monitors.

Another hazard of using SSEPs to warn of potential ischemia is the possibility of false-negative results. This may occur because of the protective effects of anesthesia and ample collateral flow. The SSEPs might be preserved during surgery, only to deteriorate postoperatively when anesthesia has worn off or the blood pressure has decreased, causing a decrease in cerebral perfusion pressure. Significant changes in the SEP occur during operations secondary to the type of anesthesia, depth of anesthesia, temperature of the patient, and so forth. It is necessary to have a knowledge of the wide range of normal values.[35]

Because of the evolution of therapy for the patient with SAH, the anesthesiologist is presented with a difficult challenge when a patient with a ruptured intracranial aneurysm comes to operation.

ANESTHETIC MANAGEMENT

Because of the change in timing of surgery for SAH, patients present for operation at a more acute stage. The patient ideally is operated on before rebleeding or vasospasm has occurred, but the patient will be suffering from the effects of the initial bleed. There are two conflicting goals for the anesthesiologist caring for the patient with SAH: first, the anesthesiologist must avoid the promotion of vasospasm and maintain the cerebral perfusion pressure within a range that maintains adequate cerebral blood flow, and second, cerebral perfusion pressure must not be allowed to increase too high so as to precipitate aneurysmal rupture.[77] Undivided attention must be paid to the cerebral perfusion pressure. Autoregulation is impaired in the region of the hemorrhage, and the tissue in the surrounding region "the ischemic penumbra," is at risk.[10] ICP must be monitored and controlled. The same is true for the arterial blood pressure because it is the other variable in the perfusion pressure equation (cerebral perfusion pressure = mean arterial pressure minus ICP). Invasive blood pressure monitoring should be instituted preoperatively. Management of the ICP includes the use of ventricular or spinal drainage, depending on the site of the hemorrhage and the area of blockage, and also loop and osmotic diuretics. The aim of the neurosurgeon in control of the ICP is not to reduce the ICP to normal levels, because this might cause the aneurysm to resume bleeding by reducing the tamponade of the surrounding tissue, but to allow perfusion of the jeopardized area of the brain. Likewise, rapid changes in the ICP are to be avoided because of renewed bleeding.

In addition to the control of ICP and the use of diuretics, the patient will be receiving prophylactic calcium channel blocking agents to prevent vasospasm. The calcium channel blockers now in use are nimodipine and nicardipine. Possible agents that may be used in the future clinically are flunarizine and nilvadipine.[93] Several potential side effects of nimodipine pretreatment are decrease in mean arterial pressure and systemic vascular resistance, increased blood and fluid requirements, decreased hypertensive response to noxious stimuli, and decreased amount of anesthesia required.[77, 88]

The patients will also be treated with anticonvulsive medications, because seizures frequently occur secondary to SAH, and steroids.[48] Steroids are often used as well to protect the normal brain and to stabilize the ischemic penumbra area.

The previous medical history of the patient will also be important. Many of the patients will have a history of hypertension or cardiac disease. This might be important because SAH quite often produces changes on the electrocardiogram that mimic ischemia and myocardial infarction.[9, 24, 41, 68, 75, 76, 90, 91] These changes can include ST-segment inversion or elevation, prolongation of QT intervals, and Q waves. Cardiac abnormalities are very common after SAH.[8, 9, 24, 29, 41, 53, 68, 75, 76, 90, 91] The most common changes seen are ST depression or elevation, changes in the T-wave morphology, QT prolongation, and dysrhythmias. The hypothesis is that vasospasm decreases flow to the hypothalamus, which leads to secretion of catecholamines and stimulation of the sympathetic pathways.[24]

The dilemma facing the anesthesiologist is whether the changes in the electrocardiogram are neurogenic or cardiogenic in origin. Neurogenic response to SAH can produce pathologic changes in the heart: subendocardial infarcts and release of isoenzymes have been observed. Patients who have pathologic changes on their electrocardiogram merit a work-up of their cardiac disease with isoenzyme studies and a thallium scan before operation if time permits. Because the need for surgery to prevent rebleeding is so urgent patients who have a positive cardiac work-up cannot have the luxury of having their operation postponed. In addition to indwelling arterial catheter, a pulmonary catheter is indicated for the operation. Another consideration in these patients would be the need for induced hypotension during the operation, with the possible detrimental effects on cardiac perfusion.

The hypothalamus may be affected also by bleeding and blood in the basal cisterns. Electrolyte abnormalities are common, and hypovolemia may occur. Hypovolemia could be very detrimental to the patient, leading to low blood pressure and decreased cerebral perfusion.[92]

Premedication of the patient who is medically stable is necessary to prevent anxiety and hypertension before the operation. The aim of the premedication is to make the patient comfortable, but we must prevent overmedication, because changes in the level of consciousness are important signs of neurologic deterioration. Also, the patient who is overly sedated will have an altered response to hypercarbia. Hypoventilation will lead to cerebral vasodilatation and increases in ICP. Patients who are not neurologically stable will not need premedication.

Induction of anesthesia in the patient with SAH is an occasion that calls on all of the skills of an anesthesiologist. Cerebral perfusion pressure must be maintained, but not at the cost of producing instability in the aneurysm. Control of blood pressure and the stress response to stimulation is important. Once the patient reaches the operative suite, they can be sedated with a short-acting agent such as midazolam. At this time, if arterial blood pressure monitoring has not been established, it must be instituted with the use of local anesthesia. There are two approaches to the control of hypertensive episodes: first, suppression of the response after it has occurred, and second, prevention of the response before it occurs. In patients with SAH the latter course is safer. Prevention of the stress response can be accomplished by the use of adequate anesthesia or antihypertensive medications before the stressful stimulus. Adequate anesthesia can take the form of intravenous agents, inhalational agents, or topical agents. Any combination of anesthetic agents may be used to achieve the desired effects, keeping in mind the effects of the anesthetics on the cerebral perfusion pressure. Intravenous agents such as barbiturates and benzodiazepines decrease cerebral blood flow and also have cerebral protective effects. They do not always prevent the response to intubation. Potent narcotics can reduce the stress resonse to intubation. Five to 10 μg/kg of fentanyl will prevent the stress response to intubation. The use of antihypertensive medications will also limit the variation in the blood pressure response generated by the stress response. Vasodilator therapy such as nitroglycerine, nitroprusside, and hydralazine may increase ICP and might be detrimental to a patient with raised ICP. β-Blockers are also used. Esmolol can attenuate the hypertensive response to intubation.[25] Labetalol is also effective in preventing the response to intubation. The patients will benefit from receiving calcium channel blocker therapy to prevent vasospasm. The calcium channel blockers also attenuate increases in blood pressure during induction.[77, 88]

Even with the best management, rupture of an intracranial aneurysm occurs during the induction of anesthesia or in the approach to the aneurysm.[17, 88] In a large retrospective study, the incidence of intraoperative rupture was 19%.[48] The most frequent times for rupture of the aneurysm to occur were predissection, dissection, and clipping of the aneurysm. If rupture occurs, the prognosis for the patient's postoperative course is worse.[17] The mortality and morbidity increases three times in those patients. To prevent rupture, it is recommended that temporary clips be used to isolate the aneurysm during the dissection, and that cerebral protective agents be used to ameliorate the ischemia that temporary clipping can produce. It is also recommended that normotension and normovolemia be used to prevent cerebral hypoperfusion during the placement of the temporary clips. Experimental evidence now supports the recommendations suggested by Batjer. With induced hypotension, an area of focal ischemia will increase in size even with the use of isoflurane to produce the hypotension.[22]

Rebleeding of the aneurysm is part of the natural process of the disease; as patients come to the operating room earlier after the first SAH, more patients with fresh rebleeding or bleeds in the operating room will be seen.[7] Even with the best care and monitoring, rebleeding still occurs. Because it is impossible to stop rebleeding until the aneurysm is clipped, it becomes imperative to be able to protect the brain from further damage.

CEREBRAL PROTECTION

Cerebral protection is covered more completely in another article in this issue. The basis of cerebral protection today is the use of barbiturate therapy. Barbiturates like thiopental, methoxital, pentobarbital, and etomidate have been shown to be effective during periods of incomplete ischemia and ineffective during global ischemia. Barbiturates decrease cerebral metabolism to the extent that they decrease cerebral function. The mechanism of barbiturate action is the prevention of synaptic discharge. Because they cannot stop or decrease the residual metabolism (maintenance of ionic gradients and so forth) in addition to stopping synaptic discharge, they can only decrease the cerebral metabolic rate by 50%. The metabolic rate cannot be decreased further by these agents, even when much larger doses of the drug are used. To have maximal effectiveness, the barbiturate is given before a potentially ischemic event. Optimal therapy would include the monitoring of cerebral function with electroencephalography, and the production of an isoelectric waveform.[16, 65, 55, 74, 94] Some of the drawbacks to using barbiturates in high doses include hypotension on administration of the drug and prolonged wake-up of the patient in whom a neurologic examination is a necessary part of postoperative care.

The volatile anesthetic isoflurane also produces a dose-related decrease in cerebral metabolic rate. Isoflurane can produce electroencephalographic suppression similar to that of barbiturate. It was hoped that isoflurane would also have the same benefits of barbiturate protection without the problem of hypotension and prolonged wake-up.[55] It is unclear at this time whether isoflurane has cerebral protective effects. In experiments performed on primates, isoflurane does not protect the brain from focal ischemia.[38, 58, 86, 87] Why isoflurane does not protect in a similar fashion to thiopental, when they both decrease the cerebral metabolic rate, is unknown at this time.

Other data support the hypothesis that isoflurane has cerebral protective effects. During carotid endarterectomies with electroencephalography monitoring for ischemia, isoflurane was shown to be protective relative to enflurane or halothane.[57] Another study on patients with SAH having surgery for removal of a cerebral aneurysm, isoflurane was used for induced hypotension. During the hypotensive period, the cerebral blood flow stayed constant while the cerebral metabolic rate decreased. When the isoflurane concentration was decreased, the cerebral blood flow increased while the cerebral metabolic rate was unchanged. The decrease in metabolic rate during the hypotensive period supports the hypothesis that isoflurane has cerebral protective properties.[52]

Other agents such as calcium channel blockers, dilantin, steroids, antioxidants (vitamin E), allopurinol, and iron chelators (desferoxamine) have all been proposed as agents to decrease cell damage and death secondary to ischemia and anoxia. None as yet have been shown to be clinically useful.[37, 56]

Central to the question of cerebral protection is the mechanism of ischemic damage. Recent evidence points to the effects of calcium and release of excitatory amino acids producing neuronal death.[72, 73] Ischemia decreases the supply of glucose, without which ATP cannot be produced. With the loss of ATP there is decreased reuptake of neurotransmitters like glutamate, an excitatory amino acid. The excitatory amino acids cause calcium levels to increase by keeping open the ion channels in the cell membrane. Influx of calcium occurs through several types of calcium ion channels. There are voltage-sensitive calcium channels (only one of the three known types is blocked by the calcium channel blockers) and agonist-operated calcium channels, activated by glutamate and other excitatory amino acids. There are two types of agonist-operated calcium channels identified, and they are linked to three types of receptors. The receptors are named for their selective agonists. One type of receptor under investigation is *N*-methyl-D-aspartate (NMDA) receptor. This receptor controls calcium entry through agonist-operated calcium channels. The receptor's natural agonist is glutamate or another excitatory amino acid.

Prevention of excitatory amino acid release presynaptically or antagonism at the receptor site currently is a fertile field of investigation in the prevention of ischemic injury. There are both competitive and noncompetitive antagonists for the NMDA receptor. Noncompetitive antagonists like MK-801, ketamine, and phencyclidine stop neuronal necrosis secondary to anoxia in cell culture.[20] Cellular uptake of calcium is prevented by the use of NMDA antagonists. It remains to be seen whether NMDA antagonists will play a role in the prevention of cerebral ischemia in the future.[19]

Until the mechanisms of cellular injury are known, it will be very hard to devise an effective therapy to prevent that injury. In the intervening time, the anesthesiologist can protect neural tissue at risk by the use of barbiturate therapy and isoflurane to decrease the cerebral metabolic rate and by the use of normotension to preserve cerebral perfusion pressure.

SUMMARY

Surgical management for SAH has advanced considerably in the last decade. With early operation, the number of patients lost to rebleeding should be greatly decreased. With calcium channel blocker therapy, and hypertensive, hypervolemic hemodilution, mortality and morbidity secondary to vasospasm should be greatly reduced. With the use of intraoperative monitoring of cerebral ischemia using electroencephalography and SSEP, and the use of cerebral protective agents and procedures, surgical morbidity and mortality should also be greatly reduced. What remains is the morbidity and mortality from the initial bleed. A large number of patients never live to see a neurosurgeon. Improvement in the diagnosis of SAH with early referral and the detection of unruptured aneurysms hold the key to a better prognosis for the treatment of SAH.[48, 49, 51]

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CEREBRAL PROTECTION, RESUSCITATION, AND
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MANAGEMENT OF SUCCESSFUL PEDIATRIC NEUROANESTHESIA

Samuel E. Kleinman, MD, and Bruno Bissonnette, MD

Anesthesia for neurosurgery presents an immense challenge to the anesthetist. Although one has little control over the patient's primary lesion, the selection of anesthetic technique and recognition of perioperative events may well have a profound effect on the reduction or prevention of significant morbidity. Current neuroanesthetic practice is based on our understanding of cerebral physiology and how it can be manipulated for patient benefit in the face of intracranial pathology. The anesthetist performing a pediatric neuroanesthetic must face the added challenge of the physiologic differences between developing children and their adult counterparts as well as a variety of procedures specific to the pediatric population. This article reviews our understanding of basic concepts in pediatric cerebral physiology and intracranial pathophysiology. A section on general anesthetic management is then presented, followed by sections on ventricular shunt procedures, myelodysplasia, supratentorial surgeries, and vascular malformations. Posterior fossa craniotomy and anesthesia for head trauma are covered elsewhere in this issue. We have designed this article to specifically address concepts and problems encountered by the pediatric neuroanesthetist and as such have avoided specific anesthetic recipes and regimens that cannot substitute for individual anesthetic judgement.

PHYSIOLOGY

Intracranial Pressure

Uncontrolled increases in intracranial pressure (ICP) constitute one of the most deleterious pathophysiologic derangements facing the anesthetist and

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efforts to control ICP are fundamental. In general, the cranium can be viewed as a closed space, occupied by brain mass (70%), extracellular fluid (10%), blood volume (10%), and cerebrospinal fluid (CSF) (10%). Increases in the volume of any one of these must be offset by a reduction in the others to maintain an overall constant volume. The brain mass itself is relatively incompressible, and changes in CSF volume serve as the primary buffer to increases in the other volumes. The point at which increases in intracranial volume can no longer be offset, results in an increase in ICP. An idealized pressure/volume relationship can be described and represents the intracranial compliance curve. Normal ICP in adults lies between 8 and 18 mm Hg, and ICP in children usually lies in the range of 2 to 4 mm Hg. Newborns may actually exhibit subatmospheric ICPs in early life.[56] Although the cranium is most easily viewed as a rigid space, the pediatric patient with open fontanelles or suture lines may be able to compensate for a slow increase in intracranial volume by expansion of the skull. Suture lines, bridged by fibrous connective tissue, are relatively difficult to separate and cannot compensate for acute increases in intracranial volume. A patient may have a normal ICP yet be at a noncompliant point on the curve, and a small change in volume will result in a large and potentially dangerous increase in ICP. This is, of course, an idealized relationship, and there is evidence to suggest that the intracranial compliance curve is a smooth logarithmic curve accounted for by the buffering of intracranial mass by the compliance of cerebral blood vessels and a pressure driven increase in CSF absorption.[8, 25, 35] Intervention on the part of the anesthetist lies in his or her ability to shift the patient's intracranial compliance curve to the right, change the slope of the patient's curve, or move the patient to a position on the left along his or her own curve.

Cerebral Blood Volume

Cerebral blood flow (CBF) is a parameter readily altered by the anesthetist and to the extent that CBF is related to cerebral blood volume (CBV), allows for reduction in ICP with reduction in CBF. Although intracranial pathology may alter or even paradoxically reverse this relationship, it is, for the most part, the clinician's most useful relationship in attempting to control ICP. Global CBF in children is higher than adults, lying between 65 and 105 mL/100 g of brain tissue.[23, 54] Premature infants appear to have somewhat lower CBF rates. CBF in gray matter is higher than that in white matter, and areas of predominant brain activity in children shift as they develop.[43] Regional areas in the brain that exhibit high levels of metabolic activity will have higher levels of blood flow. In this supply and demand relationship, as the cerebral metabolic rate of oxygen consumption ($CMRO_2$) increases or decreases, cerebral vasoconstriction or vasodilatation occurs, altering CBF in an attempt to fulfill the current demand for oxygen utilization. This phenomenon is known as autoregulation, and experimental evidence suggests that changes in local adenosine concentration in response to changes in lactate levels are responsible for this vasoactivity. As $CMRO_2$ increases, as in fever or during seizure activity, CBF will increase with a concomitant increase in CBF, and ICP will potentially increase. Conversely, hypothermia and certain anesthetic agents that decrease $CMRO_2$ will cause a reduction in CBF. During hypothermia, $CMRO_2$ and CBF decrease on the order of 7% per degree centigrade.[50]

Global $CMRO_2$ measured in children (5.2 mL O_2/100 g of brain mass per minute) is substantially greater than that measured in adults.[6, 23] The previous discussion has looked at changes in CBF from the demand side, yet important relationships exist on the supply side as well. CBF will autoregulate to maintain a constant O_2 delivery over a wide range of perfusion pressures. Adults maintain a constant CBF over a range of mean arterial pressures between 60 and 150 mm Hg.[27] Autoregulatory thresholds for infants and children are not well known, and neonatal animal models suggest that the lower limit for autoregulation may be around 40 mm Hg.[19, 48] It seems reasonable to assume that neonates with mean arterial pressures below 60 mm Hg also autoregulate, but at lower blood pressures. Evidence suggests that neonates in severe distress have altered autoregulation.[41] Above and below the limits for autoregulation, CBF changes passively with blood pressure. Blood pressure alone is an insufficient measure of cerebral perfusion. Cerebral perfusion pressure is described as the mean arterial pressure minus the central venous pressure, or in the case of the intact cranium is mean arterial pressure minus ICP when ICP exceeds central venous pressure. Again from the side of supply, anemia, hemodilution, or drugs that alter the rheologic properties of blood can increase O_2 delivery by decreasing viscosity. Adenosine levels decrease, venoconstriction occurs, and CBV decreases in the face of an overall constant CBF—a concept known as blood viscosity autoregulation. Autoregulation is impaired or abolished by hypoxia, hypercarbia, vasodilators, and high concentrations of volatile anesthetics. Intracranial pathology as the result of trauma, areas of inflammation surrounding tumor or abcess, or sites of focal ischemia exhibit altered autoregulation.

The cerebral vasculature's reactivity to hypocarbia is the anesthetist's most useful tool in reducing CBF. The CBF varies linearly with $Pa\text{CO}_2$ between 20 and 80 mm Hg. A 1 mm Hg decrease in $Pa\text{CO}_2$ results in a 4% decrease in CBF. As $Pa\text{CO}_2$ decreases, CSF pH increases, and periarteriolar changes in pH are reflected in vasoconstriction. Chronic hyperventilation results in slow movement of bicarbonate ions out of the CSF, with normalization of CSF pH and CBF within 24 hours.[50] Sudden increases in $Pa\text{CO}_2$ after hyperventilation can result in cerebral vasodilatation and increases in ICP. Experimental evidence suggests that the immature brain is relatively unresponsive to small changes in $Pa\text{CO}_2$; however, recent studies using transcranial Doppler in children show normal CO_2 responsiveness.[44] The cerebral vascular response to hypoxia is not well studied in children. Adults show no change in CBF until $Pa\text{CO}_2$ falls below 50 mm Hg, at which time CBF begins to increase exponentially.

Brain Mass

Part of the anesthetist's armamentarium contains strategies to reduce brain mass. Before the excision of a tumor, the surrounding edema can be successfully reduced with the administration of dexamethasone. Attempts can be made to reduce brain bulk by dehydration with the use of mannitol, hypertonic saline, and furosemide. In addition to its effects of promoting diuresis, furosemide may secondarily decrease ICP by reducing CSF production and reducing CVP through peripheral venodilatation. The administration of osmotically active agents is discussed in the section on fluid management.

Cerebrospinal Fluid

Most of the CSF (50%–80%) is produced by the choroid plexus lining the ventricular system. Extrachoroidal sites of production are not well identified, but studies suggest the brain's ependymal surface as well as the brain parenchyma itself are possible sites of production.[39, 46] Under normal circumstances the CSF production and absorption exist in equilibrium, with a mean production rate in children of 0.35 mL/min.[51] The composition of CSF differs from that of plasma, which suggests that it is the product of active secretion via an Na^+/K^+ dependent ATPase pump. CSF from the ventricular system exits from the fourth ventricle through the foramina of Magendie and Luschka into the subarachnoid space surrounding the brain and spinal cord. The main absorption of CSF is thought to occur in the arachnoid villi that project into the veins and sinuses of the brain. The exact mechanism of resorption is unknown, and both passive and active transport mechanisms have been proposed. Even the choroid plexus itself has been suggested as a possible site of absorption.[38] Under normal conditions the ICP is much more dependent on CBF and CBV than CSF production. Reduction of CSF production by one third has been shown to reduce ICP by only 1.1 mm Hg.[10] Therefore, it is not surprising that drugs such as acetazolamide, which reduce CSF production, have a minimal effect on ICP and become significant only in the patients whose intracranial compliance curve lies to the right. In this group of patients, anesthetic agents that increase CSF production or decrease CSF absorption should be avoided.

PATHOPHYSIOLOGY

Hydrocephalus is characterized by an increased volume of CSF within the ventricular system and is with few exceptions, caused by obstruction of CSF circulation or reduced reabsorption. The obstruction may lie within the ventricles themselves, within the subarachnoid space or at sites of CSF egress or absorption. Patients with obstructive hydrocephalus and blocked access to the arachnoid villi appear to have alternative sites of CSF absorption. There is evidence of some lymphatic type of drainage, as well as transependymal absorption.[6] Many classifications of hydrocephalus have been proposed. Inherent in all is the recognition of the degree to which ICP is increased, and an understanding of the pathophysiology responsible. Just as one may have increased ICP without hydrocephalus, one may have hydrocephalus without increased ICP.

In the newborn period hydrocephalus is usually secondary to intraventricular hemorrhage, aqueduct stenosis, or Arnold-Chiari malformation (the latter two often coexist). Premature infants frequently present with hydrocephalus secondary to intraventricular hemorrhage. Bleeding into the subependymal germinal matrix may extend into the ventricle, causing a primary blockage to CSF flow. Secondarily, an obliterative arachnoiditis may form that obstructs CSF flow even after resorption of the primary bleed.[7, 21] In the neonate, hydrocephalus may exist in the face of normal ICP as the increase in CSF volume will be compensated for by a decrease in brain mass, up to the limits of tissue compliance of the immature brain. The Arnold-Chiari malformation is most common, representing an array of abnormalities mainly in the posterior fossa and cervical region. The brain stem is displaced downward and along with an abnormal vermis extends below the foramen magnum and often well into the cervical canal. The fourth ventricle becomes compressed and its foramina may become obstructed. The cranial nerves may be stretched or entrapped secondary to this downward displacement, often presenting an array of bulbar symptoms. Hydrocephalus is present in approximately 90% of cases.

After this initial period hydrocephalus in children is most commonly caused by central nervous system (CNS) tumors. Two thirds of all childhood brain tumors occur in the posterior fossa, with an unfortunate predisposition for midline structures, and are thus frequently associated with obstructive hydrocephalus. Medulloblastomas (accounting for 15%–20% of CNS tumors in children) are usually found growing next to or within the fourth ventricle. Ependymomas, more common in the pediatric age group, are also most frequently found in the fourth ventricle. Posterior fossa tumor should be suspected in all children who present with increased ICP or cranial nerve symptomatology. Choroid plexus papillomas appear to be the only pathologic cause of CSF overproduction causing hydrocephalus.

Other diseases of childhood may predispose to hydrocephalus through a variety of mechanisms. The mucopolysaccharidoses are often characterized by an obliteration of the subarachnoid space, and achondroplastic children can present with hydrocephalus, presumably caused by occipital bone growth and impediment to venous outflow.[15, 45] In this manner, any condition that causes significant cranial deformity can lead to hydrocephalus.

COMPLICATIONS OF ELEVATED INTRACRANIAL PRESSURE

It is common to consider the cranial space as a homogenous closed box. However, it is divided into distinct spaces, with the cerebral hemispheres divided by the falx cerebri, and the posterior fossa elements separated from the hemispheres by the tentorium cerebellum. When a mass effect occurs within one compartment, extrusion of brain from one compartment to another begins when the limits of compensation or buffering have been exceeded. As a mass expands in one hemisphere, one anterior cerebral artery may be compressed as brain tissue gains egress into the opposite hemisphere under the falx cerebri. Resulting ischemia results in further edema and swelling. Herniation at this level often disrupts cortical pathways to the contralateral limbs and bladder control. Protrusion of the parahippocampal gyrus (uncus) of the temporal lobe beneath the tentorium cerebellum, through the tentorial hiatus, presents with signs of brain stem compression, progressive obtundation, ipsilateral pupillary dilatation, contralateral hemiparesis, and if uncontrolled will lead to cardiorespiratory arrest. In herniation involving the posterior fossa, the cerebellar tonsils find escape via a downward protrusion through the foramen magnum, causing compression of the medullary cardiorespiratory centers. Gross displacement of the brain through the foramen magnum may compress the vascular supply to the medulla and resulting ischemia causes Cushing's triad of tachypnea, hypertension, and bradycardia. Distortion within the posterior fossa due to a mass effect may obstruct the flow of CSF and result in obstructive hydrocephalus. Even without herniation, profound increases in ICP may result in global or regional cerebral ischemia. As ICP increases and approaches mean arterial pressure, cerebral perfusion pressure falls below critical levels. This results in tissue hypoxia, cellular injury or death, swelling from increased brain water as fluid shifts to compensate for disturbed electrolyte balance, and a vicious cycle of increasing brain volume and ICP.

GENERAL ANESTHETIC CONSIDERATIONS

In the sections to follow, anesthetic management of pediatric neurosurgical procedures is presented. Several topics common to most neuroanesthetics are reviewed before more specific discussion.

Preoperative Evaluation

Central to the neuroanesthetic is the recognition of intracranial hypertension and major neurologic deficits, which must be addressed preoperatively or during the conduction of the anesthetic. Signs and symptoms of increased ICP differ somewhat according to age group. Neonates and infants often present with a history of increased irritability, poor feeding, or lethargy. A full fontanelle, cranial enlargement or deformity, or lower extremity motor deficits are frequent signs of increased ICP in this age group.[16] Early childhood presentation of increased ICP is most often related to tumors and includes double vision, difficulty speaking or swallowing, or loss of balance. Nausea and vomiting are often present and older children complain of headache, usually in the morning. Papilledema may be present on fundoscopy. As ICP reaches critical levels, vomiting, decreased level of consciousness, cranial nerve palsies, ophthalmoplegia (loss of vertical gaze), and evidence of herniation develop.

Auscultation of the patient should address possible aspiration as well as abnormalities in respiratory pattern. Assessment of cranial nerve function and ability to protect the airway must be evaluated. Laboratory tests may yield evidence of the syndrome of inappropriate antidiuretic hormone secretion as well as electrolyte abnormalities or volume contraction from protracted vomiting. The preoperative history and chart review may reveal the need for steroid supplementation in patients with a suppressed adrenal axis from prior steroid therapy aimed at reducing tumor edema. Neurosurgical patients are often on anticonvulsant medication, and recognition of their seizure history as well as potential drug interaction is important.

Premedication

The routine use of sedation in pediatric neurosurgical patients is best avoided. Administration usually occurs far from the watchful eye of the anesthetist and may precipitate respiratory depression with attendant hypercarbia, or loss of airway maintenance. Exceptions to this rule include patients with intracranial vascular lesions, who may benefit from some degree of sedation to avoid precipitating a bleed due to hemodynamic lability.

Induction of Anesthesia

The pediatric anesthetist must frequently face the introduction of anesthesia in the patient with elevated ICP. Central to induction of anesthesia in these children is rapid control of the airway with hyperventilation to reduce CBF, avoidance of systemic hypertension associated with intubation, and a technique that will reduce the likelihood of aspiration in patients unable to protect their airway or with delayed gastric emptying. The technique we have found successful involves induction with a combination of atropine and a barbiturate, intravenous lidocaine, and a nondepolarizing muscle relaxant, followed by carefully applied cricoid pressure and manual hyperventilation. Recent study has shown that cricoid pressure and manual ventilation can be performed without insufflation of the stomach. A narcotic can be used for older children.[40] Faced with a child significantly at risk for aspiration without rapid control of the airway, the rapid intubating conditions offered by succinylcholine may outweigh its small increase in ICP. Patients without intravenous access at presentation may be induced via a small butterfly, which can often be placed with minimal patient stress or hemodynamic fluctuation. Failing this, it is probably less injurious from the standpoint of ICP to perform a skillful inhalation induction in a child than it is to subject him or her to a difficult intravenous placement. In these cases, inhalation induction is performed to a light plane of anesthesia sufficient to allow placement of an intravenous line and progression of an intravenous induction. Deep planes of anesthesia, with potential for volatile agent to induce increases in CBF. Hypoventilation and hypercarbia are best avoided.

Fluid Management

Management of fluid administration to the neurosurgical patient is dependent on the type of pathology being addressed. In the patient coming for ventricular shunt or meningocele repair, fluid management is directed mainly at replacement of third space losses. The patient with increased ICP or brain mass requires a fluid administration scheme that balances adequate intravascular volume against an effort to dehydrate brain mass. Evidence suggests that successful dehydration is accomplished by raising serum osmolality. Crystalloid solutions of low tonicity are associated with increased brain water and edema formation. Lactated Ringer's and normal saline solutions are preferred for volume replacement, and hypertonic saline is being used successfully and may indeed be a more optimal solution.

Mannitol is very useful in dehydrating brain tissue. Small doses, on the order of 0.25 to 0.5 mg/kg, are adequate to raise osmolality by 10 mOsm, which has been shown to be capable of reducing cerebral edema and ICP.[36, 42] Mannitol serves also to increase CBF and cardiac output through its reduction in blood viscosity, and as noted previously causes autoregulatory vasoconstriction.

Loop diuretics, such as furosemide and ethacrynic acid, may be useful in reducing brain edema. Although ICP does not reliably decrease after their administration alone, in conjunction with osmotic diuretics they may serve to maintain a high serum osmolality. It has been suggested that secondary brain injury may be reduced by the administration of ethacrynic acid through a decrease in glial swelling.[5] Raising serum osmolality above 320 mOsm may precipitate acute renal failure, and falling serum osmolality after a period of aggressive dehydration may result in rebound intracranial hypertension.

The ability to maintain an osmolar gradient is possible only in areas where the blood–brain barrier is intact. The blood–brain barrier is composed of the capillary endothelial cells of the cerebral vasculature, which are connected in a continuous fashion by tight junctions. This serves to form a barrier that excludes polar hydrophilic molecules. Water passes freely, followed by sodium ions over a period of several hours. Essential molecules such as glucose and amino acids cross the blood–brain barrier via carrier-mediated transport systems. Under normal circumstances, osmotic diuretics and plasma expanders such as albumin and plasma protein fraction are excluded. Unfortunately, areas that may be most useful to dehydrate, such as tumor edema, exhibit blood–brain barrier incompetence and agents of high osmolality may move into these tissues and worsen edema as water follows.[22]

Complicating an effort at brain dehydration is the requirement of maintaining adequate circulating blood volume. In many neurosurgical procedures, a substantial portion of the blood loss is on the drapes and thus difficult to quantify. Other procedures, such as resection of a vascular malformation, may require massive volume replacement. Urine output in the face of aggressive diuresis is a misleading indicator of adequate volume resuscitation, and central venous pressure monitoring may be more useful.

There is no one perfect schema for fluid replacement in neurosurgical patients with increased ICP. Most anesthetists begin osmotic diuresis at the beginning of anesthesia and observe for a brisk diuresis. As surgery and blood loss progress, volume replacement usually consists of small volumes of crystalloid, and larger amounts of colloid solutions and blood products as indicated.

Pediatric patients, particularly neonates and infants, present the additional problem of glucose homeostasis. Dextrose-containing solutions are associated with a poorer neurologic outcome and are, where possible, best avoided.[26, 47] Stressed neonates have reduced glycogen stores, and patients from the intensive care unit may have high glucose loads in their parenteral nutrition. Abrupt cessation of high-dextrose solutions can precipitate an insulin-induced hypoglycemia. In these patients, blood glucose levels should be sampled frequently, and normoglycemia maintained.

Temperature Homeostasis

Although hypothermia reduces $CMRO_2$, in general, hypothermia more often contributes to significant complications. Delayed drug clearance, slow reversal of muscle relaxants, decreased cardiac output, conduction abnormalities, attenuated hypoxic pulmonary vasoconstriction, altered platelet function, electrolyte abnormalities, and postoperative shivering are some of the complications. Intraoperative vasoconstriction leads to vasodilatation and redistribution of body heat on rewarming, with a subsequent decrease in core temperature. Every attempt to reduce body heat loss should be used in lengthy pediatric neurosurgical cases. During the induction of anesthesia and placement of intravenous lines and invasive monitors, large body surface areas are exposed. Infants and small children should be placed under radiant warmers at this time and during preparation for surgery. Extremities may be covered in plastic wrap. Dry inspired gases should be warmed and moisturized with a heat exchanger. Although the usefulness of warming blankets has been questioned, in small pediatric patients they can cover substantial body surface area and appear to work well. Procedures requiring large fluid replacement necessitate infusion through a blood warmer.

Neonates and infants, with the largest body surface area to mass ratio, are at greatest risk of hypothermia. Despite a warm operating room environment, body temperature decreases initially secondary to a redistribution of body heat from the central compartment to the periphery.[4] As body heat loss continues, pediatric patients undergo nonshivering thermogenesis in an attempt to rewarm. In the paralyzed and ventilated patient, this may be seen as an increase in body temperature and end-tidal CO_2 concentration at constant minute ventilation.[2, 3] This phenomenon may not be readily apparent and is easily overwhelmed by cooling from cold fluid administration. The exact site of temperature monitoring is for most cases less important than its reliability, and for this reason we usually select esophageal or rectal probe placement. Rewarming measures such as a forced warm air system (Bair Hugger) should continue into the postoperative period until adequate temperature homeostasis is evident.

VENTRICULAR SHUNTS

Patients for ventricular CSF shunt procedures present for a variety of indications. Often as the pediatric patient grows, the shunt must be revised, replaced secondary to malfunction, or removed due to infection. Shunt procedures are common in both severely neurologically impaired children as well as otherwise healthy patients. These children may present to the operating room several times and may request a specific induction technique. Three types of ventricular shunts are in current use: the ventriculoperitoneal, ventriculoatrial, and ventriculopleural shunts. Each has its indications and anesthetic implications.

Considerations

Several anesthetic considerations exist in the patient coming for shunt procedures, many identifiable in the preanesthetic assessment and addressed in the conduct of the anesthetic. (1) Increased ICP: Patients presenting for primary shunting, shunt revision, or malfunction may exhibit severe elevations in ICP that require aggressive treatment. (2) Full stomach: Evidence of vomiting or delayed gastric emptying are indications to rapidly secure the airway. (3) Co-existing pathology: Does the child have evidence of other significant organ system compromise, such as the cerebral palsy child with frequent aspiration? (4) Age-related pathophysiology: Is the patient likely to present problems with apnea, poor pulmonary compliance, or immature renal function?

Monitoring

Routine monitoring should consist of a precordial or esophageal stethoscope electrocardiography (ECG), blood pressure cuff, pulse oximeter, O_2 monitor, end-tidal CO_2 monitor, and temperature probe. Ventilated patients should have airway pressure monitors with disconnected alarms. Arterial line placement is usually reserved for the patient with uncontrolled ICP and hemodynamic instability.

Preinduction

The increased ICP secondary to shunt malfunction may be lowered acutely by tapping the proximal reservoir. This assumes that the malfunction has occurred distally, which is not always the case. Infiltration of the skin with local anesthetic allows the tap to proceed with minimal trauma to the patient. The needle may then be left in place to monitor ICP during induction. In the patient at risk for emesis at induction, the placement of gastric suctioning may precipitate coughing and bucking, with an undesirable elevation in ICP. Severely neurologically compromised children often have gastrostomy tubes, and these must be opened before induction.

Induction and Intubation

In the child without clinical evidence of elevated ICP, induction may proceed in any fashion with good results and we often allow children their preference. On the other hand, children with increased ICP and delayed gastric emptying are usually inducted intravenously following preoxygenation, with thiopentone with atropine, lidocaine, narcotic, and a nondepolarizing muscle relaxant. Cricoid pressure is applied and the patient is hyperventilated at low peak inspiratory pressures.

Exceptions to this procedure were discussed earlier. Laryngoscopy is a potent stimulus in increasing ICP and the trachea is orally intubated as smoothly as possible.

Maintenance

The anesthetic considerations of maintenance of anesthesia are (1) positioning, (2) ventilation, (3) anesthetic agents, (4) muscle relaxants, (5) fluid management, and (6) maintenance of body temperature. Patients are placed in a supine position with the head turned, or in a slightly lateral position. Compromised patients should be placed in a 30° head-up position, with minimal neck rotation or flexion in order to improve venous drainage. Patients often have their shunt tubing placed posteriorly before coursing to the abdomen, and those patients placed in a lateral position should have an axillary roll placed and all extremities padded.

After securing the airway, patients with increased ICP are hyperventilated to a $Paco_2$ of between 25 and 30 mm Hg. Patients with normal ICP are maintained at normocapnia. Spontaneous ventilation should be avoided in patients with ventriculopleural shunts to reduce the risk of pneumothorax, and in those with ventriculoatrial shunts to avoid air embolism during placement or whenever the cranium is opened. Neonates and infants with poor pulmonary compliance or at risk for apnea under anesthesia are mechanically ventilated.

Anesthesia is usually maintained with a combination of nitrous oxide in oxygen along with low concentrations of isoflurane and narcotic supplementation. Although nitrous oxide increases CBF in anesthetized pediatric patients,[33] it has been suggested that this increase in CBF and $CMRO_2$ caused by nitrous oxide is effectively blunted by hyperventilation and pretreatment with thiopentone. Halogenated anesthetics increase CBF, CBV, and ICP in a dose-dependent manner (isoflurane less than halothane[1, 14, 29, 30, 32]) and are therefore used in low concentrations in patients with elevated ICPs or avoided entirely until the CSF is drained.[28] Muscle relaxation is usually maintained with vecuronium or atracurium if the procedure is to be of short duration.

Ventricular shunt procedures usually do not result in significant blood or third space losses and fluid management centers around replacement of intravascular volume lost from emesis or dehydration, or alternately diuresis to acutely manage a patient presenting with high ICP.

Maintenance of body temperature is important during shunt procedures despite their relatively short duration. A large body surface area is often prepped, particularly for ventriculoperitoneal shunting, and small children can cool rapidly. Techniques to maintain temperature homeostasis were described earlier.

Emergence

Anesthetic considerations for emergence are (1) elimination of anesthetics, (2) reversal of neuromuscular blockade, and (3) delayed gastric emptying.

Before extubation of the trachea, adequate time for elimination of the anesthetic agents should be allowed, and adequate reversal of neuromuscular blockade ensured. Although not absolute insurance against regurgitation, gastric suctioning before extubation should be performed in all patients considered to have a full stomach. The patient should be fully awake with an appropriate gag reflex in order to protect the airway against emesis on emergence. Unfortunately some patients coming for shunt procedures are severely neurologically impaired and have poor airway control under the best of circumstances.

Postoperative Management

The anesthetic considerations for postoperative care are similar to those required for any general anesthetic. They include (1) oxygen and respiration, (2) maintenance of body temperature, and (3) analgesia. As with any postsurgical patient, supplemental oxygen should be placed and respiratory pattern and adequacy assessed. Neurosurgical patients in general and preterm infants less than 50 weeks postgestational age are at risk for abnormal respiratory patterns or apnea. Hypothermic patients should be rewarmed, as noted previously. Analgesics should be used judiciously and under close supervision in neurologically impaired patients. Generous use of local anesthetic skin infiltration at the time of surgery can substantially reduce the requirement for postoperative analgesia. Patients without neurologic impairment before surgery can safely be given a routine postoperative pain regimen.

MYELODYSPLASIA

Hydrocephalus is accompanied by abnormalities in the spinal column and spinal cord in up to 70% of hydrocephalic infants.[55] Myelodysplasia refers to an abnormality in the fusion of the embryologic neural groove, which normally closes in the first month of gestation. Failure of neural tube closure results in the saclike herniation of meninges (meningocele) or a herniation containing neural elements (myelomeningocele). Myelomeningoceles most commonly occur in the lumbosacral region, but failure of rostral fusion of the neural groove can result in formation of an encephalocele, which is most frequently found in the occipital or suboccipital area or nasally. Myelodysplasia results in exposed CNS structures and places the patient at extreme risk for infection (up to 95% if left untreated)[3] or injury to neural structures. For this reason, most neonates present for closure in the first 24 hours of life. A constellation of related pathologic processes can accompany the patient with myelodysplasia, frequently bringing them back to the operating theatre. For this reason, anesthetic management of both primary closure of the defect and subsequent surgeries is discussed together.

Considerations

1. Coexisting disease: What additional pathology accompanies the patient's myelodysplasia that will affect anesthetic management?
2. Age-related pathophysiology: What anesthetic considerations must be invoked during a neonatal anesthetic?

3. Airway management: Encephaloceles may present difficulty with control of the airway.
4. Positioning: Protection of the neuroplaque.
5. Volume status: High third space losses may occur from the skin defect.
6. Potential for hypothermia: Exposure of large body surface area.
7. Latex allergy: Anesthetic consideration in the patient for repeat anesthetics.

Monitoring

Adequate monitoring in the patient coming to the operating room for primary closure of a myelomeningocele includes ECG, precordial or esophageal stethoscope, blood pressure cuff, pulse oximeter, O_2 monitor, end-tidal capnography, temperature probe, and ventilator pressure and disconnect alarms. Blood loss is usually not excessive unless the sac is large and significant undermining of skin, relaxing incisions, or grafting is required for closure. For this reason, arterial line placement is rarely necessary. Patients with encephaloceles, who must undergo craniotomy for repair, should have an arterial line placed for blood pressure and hemoglobin measurement.

Preinduction

Infants presenting for repair of meningomyeloceles rarely exhibit increased ICP. The majority of myelodysplatic patients have an associated Arnold-Chiari malformation and may later develop hydrocephalus, which would require ventricular shunt placement. Concomitant syringomyelia (cavitation of the spinal cord), hydromyelia (dilitation of the central canal of the spinal cord), or diastematomyelia (division of the spinal cord by a fibrous or bony septum) may also be seen. Of concern in the older patient with myelodysplasia is the development of severe scoliosis or kyphosis with respiratory impairment. These children frequently present to the operating room for spinal instrumentation or fusion. A substantial number of these patients exhibit significant mental retardation, which may make induction difficult. Preoperative assessment of these children will show varied neurologic deficits depending on the level of the lesion. Seventy-five percent of all lesions occur in the lumbosacral region, with lesions above T4 usually resulting in total paraplegia and lesions below S1 allowing ambulation. The legs are severely affected by lesions between L4 and S1. Absence of urinary bladder and sphincter control occurs in all but the mildest cases, and patients should be evaluated for a history of hydronephrosis, chronic pyelonephritis, and renal failure.[31] Before induction of anesthesia, volume status of the patient should be assessed in light of the large potential third space losses from the exposed myelomeningocele.

Induction and Intubation

Patients with lumbosacral or thoracic myelomeningoceles may be induced lying on their left side or alternatively with their hips and back padded so as to elevate the sac above the bed. Extreme care should be taken to avoid pressure on the exposed neuroplaque and assistance should be available for induction. Infants with potentially difficult airways may be intubated after inhalation induction or alternatively by awake laryngoscopy after pretreatment with atropine. The majority of patients can be induced intravenously with thiopentone and atropine. Either a nondepolarizing muscle relaxant or succinylcholine may be used. There does not appear to be a denervation hypersensitivity with an exaggerated release of potassium in these patients, and succinylcholine has been used safely.[12] The endotracheal tube must be well secured for prone positioning. Caution should be observed when inducing patients with nasal encephaloceles because airway obstruction is common, and poor mask fit may be encountered.

Maintenance of Anesthesia

The anesthetic considerations for maintenance of anesthesia are (1) positioning, (2) ventilation, (3) anesthetic agents, (4) muscle relaxants, (5) fluid management, and (6) maintenance of body temperature.

After intubation, the patient should be carefully turned to the prone position, avoiding injury to the exposed neural tissue. Chest and hip rolls are then placed to ensue that the abdomen hangs free to facilitate ventilation and reduce intra-abdominal pressure, which may potentially increase bleeding from the epidural plexus. Because most of these children have an Arnold-Chiari malformation with cervical neurologic considerations as discussed earlier, care should be taken to avoid excessive rotation of the neck. Extremities should lie in a relaxed position and be well padded. Patients with nasal encephaloceles will undergo frontal craniotomy and are positioned as discussed in the section on supratentorial procedures.

Mechanical ventilation is used in these patients and attention must be paid to the risk of barotrauma in the immature lung. Premature infants (especially those <32 weeks and <1500 g) are at increased risk of retinopathy of prematurity and lung injury from prolonged exposure to high oxygen concentrations, and if possible, F_{IO_2} is adjusted in these patients to maintain a Pa_{O_2} of 60 to 70 mm Hg and a saturation of 90% to 95%.

Anesthesia can be maintained with a variety of agents, although narcotics and ketamine should be used cautiously because they have been implicated in an increased incidence of postoperative apnea in neonates. Neurosurgeons frequently require the use of selective nerve stimulation to identify neural structures, and in these instances muscle relaxants are avoided and potent inhalational anesthetics are used.

As noted earlier, blood loss is usually not excessive and fluid management is directed toward replacement of third space losses. Should closure of the wound be extensive and blood loss greater than usual (>10% of circulating blood volume),[5] adequate intravenous acess for transfusion must be in place.

The large area of exposed tissue, in addition to the size of the surgical prep, increases the risk of hypothermia in these patients. Active measures as mentioned in the section on temperature homeostasis should be employed. Care must be taken to prevent drying or thermal injury to the exposed neural tissue by the use of radiant warmers.

Children with a history of myelomeningocele who present for surgery appear to be at risk for the development of intraoperative anaphylaxis secondary to latex exposure. Sudden hypotension and cardiorespiratory collapse have been reported in a number of these patients and appear to be related to a history of chronic exposure to latex urinary catheters. Most episodes occur 1 to 2 hours into the surgery. Antigen testing in a series of patients undergoing orthopedic procedures who suffered an intraoperative event was positive for latex in all of the patients tested.[17, 53] A history of latex allergy should be elicited preoperatively, and exposure to latex intraoperatively in items such as Foley catheters and surgical gloves should be avoided.

Emergence

Anesthetic considerations for emergence include (1) elimination of anesthetic agents, (2) reversal of neuromuscular blockade, and (3) assessment of airway patency. Neonates at risk for apnea under anesthesia, patients with severe central neurologic deficits, or those undergoing craniotomy for encephalocele repair should be extubated fully awake after elimination of the anesthetic agents, and muscle relaxants must be adequately reversed if used. Patients with repair of nasal encephaloceles may have residual obstruction or blood in the oropharynx. These infants require careful suctioning before extubation and a close assessment of airway patency after extubation.

Postoperative Management

The anesthetic considerations for postoperative care of the patient include (1) oxygen and respiration, (2) maintenance of body temperature, and (3) analgesia.

Supplemental oxygen should be placed on all patients until adequacy of respiration is ensured. As noted previously, neonates are at increased risk for apnea and periodic breathing postoperatively. Active warming measures are continued postoperatively until temperature homeostasis is event. Narcotic analgesics are used cautiously in the immature patient and those with significant central neurologic deficits.

Older patients returning for surgery often have a significant sensory deficit below their lesion and should be positioned carefully during long postoperative recovery to avoid pressure injuries.

SUPRATENTORIAL PROCEDURES

Supratentorial procedures include a wide variety of neurosurgical indications. The following presents a common anesthetic approach, followed by emphasis on special aspects of anesthesia for craniofacial procedures, craniosynostosis, hypophyseal surgery, and seizure disorders. Anesthesia for vascular pathology follows in a later section.

Supratentorial Craniotomy

Brain tumors constitute one of the most common indications for craniotomy in children, with approximately one third of all tumors residing above the tentorium.

Considerations

1. Increased ICP: The extent to which ICP is elevated must be recognized.
2. Full stomach: There is delayed gastric emptying in the child with intracranial pathology.

3. Electrolyte and fluid problems: Hydration state and electrolyte balance may be altered in the child with intracranial pathology and the syndrome of inappropriate antidiuretic hormone secretion.
4. Age-related pathophysiology: Anesthetic considerations are identical to those discussed in earlier sections.

Monitoring

Routine monitoring consists of a precordial or esophageal stethoscope, ECG, blood pressure cuff, O_2 monitor, and temperature probe. End-tidal CO_2 and pulse oximetry should be used, and ventilated patients require airway pressure monitors and disconnect alarms. All patients in our institution receive arterial line placement for hemodynamic monitoring, blood gas evaluation, and blood chemistry sampling. Patients in whom blood loss will be significant, those with expected hemodynamic instability, or those at increased risk for air embolism receive central venous catheters.

Preinduction

Determination of the degree to which ICP is elevated in patients undergoing craniotomy is essential. Patients with large mass lesions and significant tumor edema, or obstruction to CSF outflow require an anesthetic approach aimed at reducing ICP. Some children may undergo ventriculostomy placement before their definitive surgical procedure and can be managed in the manner discussed in the earlier sections. Preoperative neurologic deficits should be evaluated and documented. Intracranial pathology of many kinds, such as tumor or inflammation, can present with the syndrome of inappropriate antidiuretic hormone. Evaluation of the child may show evidence of hyponatremia, low serum osmolality, high urine osmolality, and oliguria. Edema is rarely present. Preoperative treatment usually consists of fluid restriction and occasional pharmacologic therapy.

Induction and Intubation

Unlike children with normal ICP, induction followed by a minimally stimulated rapidly secured airway and hyperventilation is of paramount importance in the patient with significantly elevated ICP. Induction generally proceeds as discussed in the section on ventricular shunts, with intravenous thiopentone, lidocaine, narcotic, and a nondepolarizing muscle relaxant. Cricoid pressure is applied and the patient hyperventilated with low peak inspiratory pressures to avoid inflation of the stomach. Laryngoscopy should proceed as smoothly as possible, and any increases in heart rate or blood pressure may require discontinuation of the intubation attempt until anesthesia can be deepened. Some anesthetists prefer nasotracheal intubation for the patient in whom postoperative ventilation is expected or in small infants where the tube may be better stabilized.

Maintenance

The considerations for maintenance of anesthesia include (1) ventilation, (2) positioning, (3) anesthetic agents and muscle relaxants, (4) fluid management, and (5) maintenance of body temperature.

Patients with increased ICP are generally ventilated to a $Pa{CO_2}$ of between

25 and 30 mm Hg. Occasionally, a very "tight brain" with uncontrollable hypertension can require lower levels of $Paco_2$. Caution must be exercised, because hyperventilation-induced vasoconstriction may decrease cerebral perfusion pressure and possibly lead to ischemia or alternately shift blood flow to hyperemic brain with impaired autoregulation. Positive end-expiratory pressure is generally avoided to facilitate cerebral venous drainage. The use of positive end-expiratory pressure may also decrease mean arterial pressure, and this should be considered in patients with decreased cerebral perfusion pressure. In patients with impaired oxygenation, small amounts of positive end-expiratory pressure should be gradually increased to the minimum necessary to correct hypoxia so that there will be the least possible impediment to venous return.

Pediatric patients are usually placed supine for supratentorial procedures, with the head elevated 30 degrees to facilitate venous drainage. Extremities should be well padded and the eyes protected from injury. Care must be taken to avoid undue flexion, extension, or rotation of the neck. The anesthetist should carefully assess the position of the patient to ensure that the head does not support the body or vice versa. Prone positioning is discussed in the article on posterior fossa surgery by Mayberg and Lam.

Discussion of the specific pharmacology of each anesthetic agent is beyond the scope of this text. Agent selection should be rational, having a basis in the wide body of clinical and laboratory data compiled in this area. Although some of the data are conflicting or controversial, our approach appears to conform to a majority opinion, if there is such a thing. To this end, we select either of two techniques: one, neurolept, and the other, a balanced inhalational approach. The neurolept technique combines nitrous oxide, a synthetic short-acting narcotic (usually fentanyl citrate), and a nondepolarizing muscle relaxant, with either a benzodiazepine or droperidol. With a balanced approach, sub-MAC concentrations of isoflurane are used with nitrous oxide, fentanyl, and a nondepolarizing muscle relaxant. Any nondepolarizing muscle relaxant is likely acceptable for the neurosurgical patient, and we prefer pancuronium for its vagolytic properties and lack of histamine release, which could potentially increase ICP.

Fluid management for the patient undergoing craniotomy can be very problematic. Patients with increased ICP often receive a brisk mannitol-induced diuresis, potentiating the possibility of intravascular volume collapse, especially in light of the often substantial blood loss during skin incision and excision of the bone flap. The central venous pressure monitoring can be a valuable aid and volume expansion is usually with colloid solutions. Simple craniotomy in patients without significantly increased ICP and in procedures with manageable blood loss frequently receive crystalloid replacement only, with good results.

Efforts to maintain body temperature should be performed as outlined previously, especially with respect to warming of fluids. Rapid infusion of cold fluids during periods of brisk bleeding can precipitously lower body temperature to dangerously low levels.

Emergence

Anesthetic considerations for emergence include (1) elimination of anesthetic agents, (2) reversal of neuromuscular blockade, (3) delayed gastric emptying, and (4) increased ICP. The decision to extubate the trachea at the end of the procedure is made on the basis of the success of the surgical intervention, smoothness of the intraoperative course, normalization of ICP, age of the patient, and the degree of residual neurologic deficit and how it will affect respiration and airway protection. Patients without adequate respiratory effort will retain CO_2 with the potential for increased ICP. A gag reflex should be present for airway protection. Children remaining sedated and hyperventilated into the postoperative period should be suspected of having increased ICP. Neonates with poor pulmonary compliance or an immature respiratory drive may remain intubated postoperatively. Barring such adverse complications, the child can be extubated awake after reversal of neuromuscular blockade and elimination of anesthetic agents.

Postoperative Management

Considerations for postoperative management after supratentorial craniotomy include (1) oxygen and respiration, (2) temperature homeostasis, (3) analgesia, (4) neurologic assessment, (5) hypertension, and (6) seizures.

As with any postsurgical patient, supplemental oxygen should be supplied and adequacy of respiration assessed. Patients requiring postoperative ventilation will require adequate sedation and possibly muscle relaxation to avoid agitation and increased ICP. Efforts to maintain body temperature should also continue postoperatively as noted earlier. The use of local anesthetic skin infiltration intraoperatively or a cervical superficial plexus blockade at the end of the procedure can reduce the requirement for postoperative analgesics. Analgesic use must be balanced between patient comfort and the ability to follow the patient's neurologic status. An obtunded patient must be evaluated for increased ICP and surgically correctible pathology such as intracranial bleeding and should not be written of as "sleepy from the narcotic."

The most common contributor to postoperative increased ICP is uncontrolled hypertension. Once postoperative pain control has been reached, blood pressure can be controlled with the use of vasodilators, remembering that these drugs can also dilate the cerebral vasculature. β-Blocking drugs have been used successfully, particularly labetolol with its combined β- and α-blocking properties, and do not normally cross the blood–brain barrier.[13]

Seizures frequently appear in the postoperative course and may occur in the recovery room. Many surgeons place their patients on preoperative anticonvulsants and continue these into the postoperative period. Phenobarbital appears to be the most frequently used drug, and phenytoin or other medications are added for refractory patients.

Craniosynostosis

Special considerations for patients with craniosynostosis include (1) increased ICP and (2) blood loss. Children and infants undergoing craniectomy should have an evaluation for evidence of increased ICP, and induction should proceed as discussed earlier. The degree of blood loss is increased in patients with multiple suture craniosynostosis and in children over 6 months old with thicker bone tables. Most craniosynostosis surgery is performed between 2 and 6 months of age, a period that coincides with the physiologic hemoglobin nadir. Transfusion may therefore be required to maintain an acceptable hemoglobin level. Simple suture craniectomy in the young child with normal ICP does not always require arterial line placement. As bleeding can be early and brisk, adequate intravenous access for fluid and blood replacement must be available. Children with elevated ICP and those undergoing extensive multiple suture procedures usually receive arterial line placement.

Craniofacial Procedures

Special considerations for craniofacial procedures include (1) difficult intubation, (2) blood loss, and (3) extubation and airway edema. Many craniofacial procedures require frontal bone advancement or reshaping and, as such, constitute intracranial surgery. Efforts to reduce brain bulk are often helpful to the surgeon and proceed as discussed earlier. Occasionally, a lumbar subarachnoid drain is placed for continuous CSF drainage.

Patients undergoing craniofacial procedures present a multiplicity of problems with intubation, which can include mandibular hypoplasia, immobile neck or trachea, macroglossia, and poor mouth opening. Few children can tolerate awake laryngoscopy or awake fiberoptic intubation, and the mainstay of induction in the difficult pediatric airway is inhalation induction. After successful induction, direct laryngoscopy or fiberoptic intubation (in endotracheal tubes >4.0) can usually be accomplished. Help should always be available for difficult intubations as well as equipment for surgically securing the airway. After placement of the endotracheal tube, it should be wired to the mandible by the surgeon, and the eyes lubricated and sewn closed with a tarsorrhaphy stitch. Mono-bloc procedures require intraoperative replacement of the tube nasally.

Craniofacial surgery often includes multiple suture craniectomies, dissection of large skin flaps, as well as facial bone advancement, resulting in copious blood loss on the order of 0.5 to 1.5 blood volumes.[11] A hypotensive anesthetic technique is frequently employed to reduce blood loss. These patients should receive placement of at least two large-bore intravenous lines along with an arterial line and urinary catheter placement. Central line placement is often very helpful for managing fluid replacement and aspiration of intracardiac air should air embolism occur. Patients in whom air embolism is likely require precordial Doppler monitoring. Management of air embolism is thoroughly discussed elsewhere in this issue.

Patients undergoing facial procedures below the orbits frequently have significant edema of their upper airway structures and will remain intubated for at least 24 hours while waiting for resolution. In our institution, the patients having extensive frontal craniotomies remain intubated, sedated, and ventilated with subarachnoid drains in place for 24 to 48 hours postoperatively in an effort to reduce CSF leakage through the dura. Before extubation, the patient should be fully awake and carefully but thoroughly suctioned to remove any clots and residual blood in the oropharynx.

Craniopharyngioma

Special considerations for craniopharyngioma surgery include (1) positioning, (2) hypopituitarism, (3) diabetes insipidus, (4) altered insulin requirement, (5) hyperthermia, and (6) seizures.

Craniopharyngiomas are benign encapsulated intracranial tumors. Children frequently present with symptoms of some form of endocrine failure or with signs of visual disturbance or hydrocephalus as the tumor grows beyond the sella tursica and compresses the optic chiasm or other midline structures. The transphenoidal approach is rarely used in pediatric patients, and the majority of craniopharyngioma resections are performed via frontal craniotomy. Anesthesia for craniopharyngioma and hypothalamic tumor surgery is similar to that for supratentorial craniotomy.

Preoperative evaluation of the child with craniopharyngioma centers on the recognition of the presence of hydrocephalus and the elucidation of endocrine dysfunction, which could affect anesthetic management. Children may present with symptoms of hypothyroidism, growth hormone deficiency, adrenocorticotropic hormone deficiency, or diabetes insipidus.[24] Replacement may be necessary preoperatively with thyroid hormone and both preoperatively and intraoperatively with steroid.

Diabetes insipidus of central origin is secondary to the disruption of antidiuretic hormone–secreting cells. Rarely present preoperatively, it frequently presents in the immediate postoperative period. Patients exhibit high urine output, high serum osmolality, and low urine osmolality, becoming hypernatremic and hypovolemic. Therapy consists of fluid replacement with hypotonic solutions, replacement of lost electrolytes, and administration of vasopressin or one of its analogs such as 1-deamino-(8-D-arginine)-vasopressin. Additionally, steroid, thyroid, mineralocorticoid, and sex hormone supplementation is required postoperatively. Insulin-dependent diabetic patients may have reduced insulin requirements after surgery, and their blood glucose levels must be closely monitored and their insulin regimens altered.[49]

Other problems arising in the postoperative period include seizures and hyperthermia. Adequate surgical exposure often requires significant retraction of the frontal lobes, and anticonvulsant prophylaxis is frequently begun intraoperatively and continued into the postsurgical period. Injury to the hypothalamic thermoregulatory mechanisms may result in hyperthermia. Efforts should be made to maintain normothermia and reduce the risk of hypermetabolic cell injury.

Seizure Surgery

Specific anesthetic considerations for seizure surgery include (1) the awake patient, (2) analgesia, and (3) airway maintenance. The conduct of an anesthetic for excision of a seizure focus is most challenging. It requires an awake and responsive patient to facilitate identification of the appropriate surgical site and to avoid damage to uninvolved structures. The mainstay of anesthetic technique for this type of surgery is a neuroleptanalgesia. Induction of anesthesia is performed with a neuroleptic agent such as droperidol given once to avoid impairment of the patient's ability to cooperate during surgical removal of the seizure focus. Fentanyl citrate is used until acceptable analgesia is obtained. The administration of N_2O in O_2 by mask can be used as adjunct to the intravenous analgesia until cortical mapping is performed. Arterial and central line placement is accomplished with local anesthetic infiltration. Generous local anesthetic infiltration is performed during placement of the pin holder and before skin incision.[18] Supplemental oxygen is placed and occasionally nitrous oxide is added to reduce discomfort during excision of the bone flap. Analgesia is supplemented throughout the procedure with additional doses of fentanyl. Care must be taken to avoid obtundation, respiratory depression, and an unusually high $Paco_2$.

We have found this technique acceptable in children above 4 years of age. Younger pediatric patients are usually unable to cooperate or require intubation for airway protection. Limitations of the technique include (1) restlessness in children who must remain motionless for a long period in an uncomfortable position, (2) breakthrough pain during dural manipulation and electrocautery, and (3) poor cooperation in the psychologically disturbed child with seizure disorder.

CEREBRAL ARTERIOVENOUS MALFORMATIONS

Arteriovenous malformations (AVMs) are uncommon congenital or acquired lesions. Congenital AVMs arise from the abnormal development of the arteriocapillary network connecting the arterial and venous systems. These lesions likely occur secondary to maldevelopment occurring before the embryologic formation of adult arterial wall structure, although the exact etiology is unknown. Flow of blood through the low-resistance arteriocapillary circuitry results in progressive distension and dilatation of the entire venous system of the brain and cranium.[37] Most AVMs go undetected until the fourth or fifth decade of life and only 18% present below the age of 15 years. Cerebral injury is probably secondary to one or more causes: (1) hemorrhage with thrombosis and infarction; (2) compression of adjacent neural structures; (3) parenchymal ischemia caused by steal of blood flow to the low-resistance network; (4) congestive heart failure (CHF) and hypoperfusion; and (5) surgical disruption or diversion of blood flow. Patients with AVMs may undergo interventional radiologic attempts at embolization of the arterial blood supply or stereotactic radiosurgery as definitive or adjunctive therapy. Surgical clipping may be performed as a single or staged procedure.

Considerations

The following are considerations for patients undergoing AVM resection: (1) Preexisting pathophysiology: Does the patient present with increased ICP or CHF? (2) Age-related pathophysiology: Will organ system immaturity impact on the anesthetic technique? (3) Blood loss: Anesthetic management must address the possibility of significant blood loss.

Monitoring

Routine monitoring includes the use of a precordial or esophageal stethoscope, ECG, blood pressure cuff, pulse oximeter, end-tidal capnograph, O_2 monitor, temperature probe, and ventilator alarms. Arterial line placement is essential and central venous pressure monitoring is almost always used on all but the smallest AVMs. Patients receive urinary catheter placement after induction.

Preinduction

Presenting symptomatology can vary among children of different age groups and as such require a thorough evaluation for pathophysiology that may complicate the anesthetic. Older children most commonly present with evidence of subarachnoid hemorrhage or intraventricular hemorrhage. Over 70% of pediatric patients presenting with spontaneous subarachnoid hemorrhage have AVMs as the causative etiology. Seizures are the presenting symptomatology in approximately 25% of patients, who may be on anticonvulsant therapy. Infants commonly are referred for evaluation of hydrocephalus and must be evaluated for evidence of increased ICP. The neonatal presentation of cerebral AVM is the most challenging because it is often associated with CHF.

The low-resistance pathway of the AVM results in volume overload and signs of right-sided heart failure. The CHF rarely presents in utero, and patency of the ductus arteriosus may supply a pressure release for the right ventricle by pumping into the low-resistance placental circuitry. The increased demand for cardiac output as well as increased pulmonary blood flow as pulmonary vascular resistance decreases may precipitate left ventricular failure. The low-resistance circuit of the cerebral AVM results in low systemic diastolic pressure and combined with an increased left ventricular end-diastolic pressure from overload results in reduced coronary perfusion pressure and myocardial ischemia.[21] Right-to-left ductal shunting may occur and can comprise a majority of descending aortic blood flow as left ventricular output is diverted to the cerebral circulation. Also, an increased systemic venous return can produce right-to-left shunting at the atrium level. Pulmonary vascular resistance increases with continued high right ventricular output. It can then be seen that cardiac failure in these infants is secondary to both pressure and volume overload. Therefore, it may present with a picture similar to persistent fetal circulation.[9, 34] Physical examination will elucidate signs of left- and/or right-sided heart failure such as tachypnea, tachycardia, cyanosis, pulmonary edema, hepatomegaly, and ECG changes. Laboratory studies should be evaluated for evidence of electrolyte imbalance such as hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, and pH imbalance, often in light of aggressive diuretic therapy. Neonates in CHF often receive digoxin therapy, and patients in severe failure are intubated, mechanically ventilated and will be on inotropic support. Patients without evidence of CHF or obtundation from increased ICP can be premedicated to reduce agitation and hypertension before induction and possibly reduce the chance of initial or rebleeding.

Induction and Intubation

Central to induction of anesthesia in children with AVM without CHF is prevention of hypertension during laryngoscopy. Inhalation or intravenous induction may be performed in the child without evidence of increased ICP. Incremental doses of intravenous induction agent and narcotic are given along with lidocaine before laryngoscopy. A nondepolarizing muscle relaxant is indicated. A careful application of graded stimuli should precede laryngoscopy and depth of anesthesia is evaluated. Laryngoscopy is abandoned and anesthesia deepened if tachycardia or hypertension are evident. Patients with increased ICP are induced in similar fashion, using a modified rapid sequence approach as discussed in earlier sections. Neonates in CHF will have intravenous access in place before induction. Extreme caution must be observed because many anesthetic agents used during induction, including lidocaine, are myocardial depressants and may precipitate cardiovascular collapse. Oral or nasal intubation may proceed as the anesthetist prefers.

Maintenance of Anesthesia

Considerations for maintenance of anesthesia include (1) positioning, (2) ventilation, (3) anesthetic agents, (4) blood loss and fluid management, and (5) temperature maintenance.

Positioning for surgery is dependent on the site of the malformation. The AVMs most commonly receive their blood supply from the middle meningeal artery distribution, and are approached from a supine position. Prone or lateral positioning may be used for AVMs of differing location.

All patients are mechanically ventilated for control of $PaCO_2$. Patients with hydrocephalus may require some degree of hyperventilation until the pressure is relieved. It is our practice to maintain normocarbia in most children undergoing AVM resection, based on the supposition that hypocarbia will decrease CBF in normal vessels and shunt flow to the low resistance and CO_2 unresponsive malformed vessels. This could result in ischemia of brain parenchyma and increased bleeding from the AVM.

Anesthetic agents selected for maintenance are similar to those used for any intracranial procedure. In addition, a hypotensive technique is employed at time of ligation of the AVM. A variety of agents can be used, including trimethaphan, nitroprusside, nitroglycerine, and high concentrations of isoflurane. We have found phentolamine infusion to be very useful and easily titratable. Although isoflurane may have some cerebral protective effect, it can increase CBF at high concentrations and is not as easy to titrate as intravenous agents. Neonates in CHF are frequently on inotropic support and cannot tolerate hypotensive anesthesia. CHF is of the high output type, and systemic vascular resistance in these patients is usually low. Vasoactive drugs should be infused via central lines if possible.

Fluid management in these patients can be very difficult. Neonates may not tolerate fluid loads at all, and children with contracted intravascular compartments from attempts at brain dehydration may experience rapid circulatory collapse following brisk intraoperative bleeding. Patients undergoing AVM resection should have at least two large bore intravenous lines with blood pumps in place before surgery.

Maintaining body temperature can be quite difficult in children, especially during massive transfusion. Strategies to maintain body temperature are employed as described earlier. We try to allow the patient's core temperature to go no lower than 34°C, as a compromise between lowering $CMRO_2$ and preventing the deleterious effects of hypothermia.

Emergence

Considerations for emergence from anesthesia include (1) elimination of anesthetic agents, (2) reversal of neuromuscular blockade, and (3) assessment of airway patency and respiration. In patients without a history of CHF, following elimination of anesthetic agents and reversal of neuromuscular blockade, the patient is assessed for return of airway reflexes and adequate respiratory effort. Awake extubation can then proceed. Patients with a likelihood of significant neurologic deficit, extensive resection or brain retraction, or cerebral edema remain sedated and intubated into the postoperative period.

Postoperative Management

The anesthetic considerations for postoperative care include (1) oxygen and respiration, (2) maintenance of body temperature, (3) analgesia, and (4) hypertension. Extubated patients receive supplemental oxygen and frequent reassessment of respiratory status. Infants are at increased risk for apnea and respiratory embarrassment. Active warming measures should continue postoperatively as required, until evidence of temperature homeostasis is evident. As with any intracranial procedure, narcotic analgesics must be used cautiously to avoid obtundation and respiratory depression. Patients require constant observation for evidence of postsurgical rebleeding, which would require immediate reexploration. In conjunction with analgesics, antihypertensive therapy may be required to avoid sudden increases in blood pressure that could precipitate rebleeding. Children undergoing surgery for AVM resection are frequently on anticonvulsant therapy to suppress seizure activity or as prophylaxis. These medications should be continued into the postoperative period.

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ENERGETICS OF CEREBRAL METABOLISM AND ION TRANSPORT

Philip E. Bickler, MD, PhD

The analysis of the structure, physiology, and function of the human brain represents one of the most complex of all biologic problems. A major aspect of this complexity is the myriad synaptic connections, voltage and ligand-gated ion channels, and intracellular second messenger systems that mediate interneuronal communication. The energy required to maintain and regulate these systems is considerable. The mammalian brain weighs but 2% of body weight yet consumes an amount of ATP equivalent to 20% of that produced by the entire body. This high metabolic activity is necessary for the complex integrative function of the mammalian brain, but renders neural tissues particularly vulnerable to depletion of energy reserves.

This article explores the relationship of energy metabolism to neural function in the mammalian brain, identifies how the unique features of mammalian cerebral metabolism support neural function, and explores the metabolic and physiologic responses of neurons to threatened energy depletion. The primary emphasis is the regulation of energy metabolism, the energetic costs of ion transport, and the impact of anesthetics, hypothermia, and acid–base disturbances on these processes.

CEREBRAL ENERGY METABOLISM: OXIDATIVE AND GLYCOLYTIC ATP GENERATION

Under normal conditions, D-glucose is necessary for cerebral function in all higher animals, because the central nervous system (CNS) (as well as the renal medulla, testes, erythrocytes, and embryonic tissues) requires D-glucose

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as the sole or major source of metabolic fuel and to generate Krebs' cycle intermediates needed for metabolism of other substrates. Glucose depletion rapidly leads to coma and eventually to brain death. Therefore, it is somewhat paradoxical that very little glucose or glycogen is stored in the mammalian brain: muscle stores 10 times as much glycogen and liver has 100 times as much glycogen per unit mass. The glycogen storage capacity of the brain is sufficient to last less than 3 minutes at normal rates of ATP consumption. The brain is thus almost entirely dependent on the circulation for the 120 g of glucose it requires each day. It is interesting to note that in animals known to be particularly resistant to the effects of oxygen deprivation (e.g., turtles, diving mammals, and neonatal mammals) brain glycogen stores are greater and thus longer periods may pass until energy stores are depleted.

The mammalian brain is sustained by glucose stored in the form of glycogen in the liver, muscle, and to a lesser extent other organs. Glycogen stored in the liver is quantitatively the most significant source of glucose during fasts of 24 to 48 hours. D-glucose is also synthesized de novo from glycolytic intermediates, amino acids, glycerol, and Krebs' cycle intermediates in the process of gluconeogenesis. In mammals, gluconeogenesis occurs largely in the liver and to a much smaller extent in the renal cortex, but does not occur in the brain to any appreciable degree. Gluconeogenesis occurs only under aerobic conditions and is energetically costly because it requires 2 mol of lactate, 4 mol of ATP, 2 mol of GTP, and 2 mol of NADH to yield 1 mol of glucose.[20] Gluconeogenesis is essential for cerebral function under starvation conditions because some basal input of glucose is required to sustain the pool of Krebs' cycle intermediates necessary for metabolism of ketone bodies.

Energy derived from the cerebral oxidation of ketones is important in neonates under normal conditions and during starvation in adults. Ketones were first recognized as metabolic substrates for the brain in the 1960s by observing that blood glucose in obese humans was drastically reduced by a fast of 40 days, whereas plasma B-hydroxybutyrate and acetoacetate reached high levels.[4] It is now known that normal humans fasting only 12 to 16 hours show a significant increase in the cerebral uptake of ketone bodies, directly proportional to the ketone content of the blood[11] and apparently due to induction of specific ketone transport systems. During starvation, more than half of the oxygen used by the brain is the result of oxidation of ketone bodies. Despite the importance of ketones to cerebral metabolism, only glucose or compounds readily converted to glucose can revive mammals from hypoglycemic coma. None of the ketones alone are effective, probably because glucose is necessary to provide sufficient levels of Krebs' cycle intermediates to facilitate their metabolism.

D-Glucose enters the brain through facilitated transport (i.e., it is conveyed through specific membrane-based transporters that exhibit the properties of saturability and competition). In the intact brain, the blood–brain barrier restricts the metabolic substrates used by the brain to a relatively few compounds (e.g., glucose, ketone bodies, lactate). In situations without an intact blood–brain barrier (e.g., brain slice preparations or possibly certain pathologic states) the metabolic repertoire of the brain is wider, and compounds such as various Krebs' cycle intermediates and dicarboxylic acids, which are usually unable to pass an intact blood–brain barrier, can be metabolized.

Once in the cell, glucose undergoes glycolytic and oxidative metabolism to yield CO_2, water, and energy in the form of ATP:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + 34\text{–}36\ \text{ATP} \qquad (1)$$

Glycolysis, occurring anaerobically in the cytoplasm, yields 2 mol ATP per mol of glucose, and oxidative phosphorylation, occurring in the mitochondria, yields 30 ATP directly, and 6 mol ATP from 2 mol NADH generated in the cytosol during glycolysis. The complete oxidative metabolism of glucose thus yields 17 to 18 times as much ATP energy as does glycolysis alone. Molecular oxygen (O_2), the terminal electron acceptor in the mitochondrial electron chain, is required to sustain the full yield of ATP from glucose; without O_2 only 2 mol ATP per glucose are realized. Oxygen limitation is critical because of (1) limited glycogen stores in the mammalian brain, (2) the inability of the mammalian brain to maintain ionic homeostasis under energy-limiting conditions, and (3) because accumulation of hydrogen ions, lactate, and other osmotically active intermediates may be toxic. In contrast, in lower vertebrates and to some extent in neonatal mammals, anaerobic glycolysis has the potential for sustaining ATP production at rates compatible with maintaining cellular integrity for considerably longer periods. Factors contributing to this may include reduced energy requirements during hypoxia and greater glycogen stores.[7, 15] Metabolic strategies that enhance survival under energy-limiting conditions are discussed in the following sections.

The basal rate of glucose use in the mammalian brain is roughly 0.3 to 0.8 mol/g wet weight per minute. This corresponds to an ATP synthesis rate of 11 to 28 μg ATP per minute per gram. This rate is much higher than the value of 6 to 9 μmol ATP per minute per gram in the heart.[32] Cerebral metabolism is much higher in smaller animals (metabolic rate scales with the two thirds power of body mass in all animal groups and ectothermic animals have a metabolic rate one fifth to one tenth that of mammals of a given size), and white matter consumes less glucose than gray matter. Oxygen consumption varies directly with the rate of glucose consumption and increases regionally with activation of specific neuronal groups, e.g., the visual cortex increases glucose consumption during visual processing. Combustion of 1 mol of glucose requires 6 mol of O_2, and by measuring oxygen consumption and glucose use it may be calculated that 95% of the carbohydrate consumed by the brain undergoes oxidative metabolism. This is consistent with the measurement that lactate production by the CNS under aerobic conditions accounts for only 0% to 4% of glucose used.[20] This means that of the roughly 25 μmol ATP per minute per gram produced under nonstimulated conditions, less than 1% is derived from glucose terminally metabolized to lactate.[9] The brain is thus an intensely metabolizing organ that normally derives essentially all its energy from oxidation of glucose. During anoxia, of course, all of the ATP produced must come from glycolysis alone.

REGIONAL DIFFERENCES IN CEREBRAL METABOLISM

There are important metabolic differences between different types of cells in the CNS. For example, although white and gray matter concentrations of ATP, ADP, AMP, or phosphocreatine (PCr)[35, 49] are similar, gray matter has a significantly higher turnover of these high energy intermediates. Important metabolic differences between neurons and glia exist, but surprisingly few details are known. Even among different subtypes of glia there may be significant differences, e.g., different astrocyte subtypes may be metabolically distinct, possess different types of membrane glutamate receptors, and have different sensitivities to hypoxia.[18] It is likely that many other important differences remain to be defined.

An important method for studying regional metabolism of the brain is measurement of radiolabeled glucose uptake. Direct autoradiography of different brain regions after administration of 2-^{14}C-glucose has made possible estimates of regional glucose use in rat brain over short intervals (5 minutes). Short interval study is necessary to visualize the localized uptake of isotopic glucose and accumulation of glucose 6-phosphate, because the glucose is further metabolized and the remaining label removed by the circulation.[38] With this technique, the relationship of regional glucose use to neuronal activity was first clearly established.

Another powerful tool for evaluating regional cerebral metabolism is deoxyglucose uptake. The technique depends on the accumulation of radiolabeled ^{14}C-2 deoxyglucose (2-DG), which is taken up by the brain glucose transport system and is converted to 2-deoxyglucose-6-phosphate, where its metabolism is arrested. The trapped metabolite is quantified by autoradiographic densitometry applied to tissue slices prepared after sacrificing the animal by decapitation and freezing the brain. Although there is some controversy about the rapidity of dephosphorylation and removal by the blood,[13] the functional response of 2-DG to different stimuli can be readily demonstrated. For example, application of olfactory stimuli produce a marked increase in 2-DG-6-P in the olfactory bulb in the rat, and auditory stimuli cause similar responses in the auditory nuclei and cortex. The 2-DG technique has also been applied in vivo with the positron-emitting radionuclide 2-^{18}F-2-deoxyglucose. The fluoro-2-DG accumulates, albeit at lower efficiency, in the same manner as 2-DG. During different functional states, computed tomography has been used to compose spectacular three-dimensional representations of regional glucose use in the brain.

The techniques mentioned previously can identify metabolic activity only in rather large groups of neurons. An alternative technique capable of identifying individual neurons that have been metabolically active in the *c-fos* immunocytochemical menthod. This postmortem method relies on staining cells that have been metabolically active during life and have expressed the protein *c-fos*. This technique has recently been used to identify individual neurons responsible for carbon dioxide sensitivity in the medullary chemoreceptors.[40]

CEREBRAL ENERGY PRODUCTION DURING THREATENED ENERGY FAILURE

Because sustained energy production is vital to the survival of neural tissue, it is not surprising that considerable effort has been expended to analyze cellular responses to threatened energy failure. Several fundamental principles underlie almost all of our understanding in this area. First, in order for the brain to sustain function during periods of oxygen or substrate deprivation, provision must be made to use fermentable sources of storage energy to maintain ATP levels. In mammals, the only significant way this occurs is via glycolysis. Second, in order to sustain ATP synthesis under hypoxic conditions, each oxidative step in glycolytic metabolism must be balanced by a reductive one, i.e., oxidation-reduction potential must be maintained.

Among the most important physiologic adjustments that occur during hypoxia are those mechanisms that regulate intracellular ATP levels. Essentially, the issue is how free cytosolic adenine nucleotides are provisioned to the machinery required for maintenance of cellular integrity (chiefly, membrane ion pumps). First, we must understand something about bound and free ATP concentrations in the cell. Murphy et al[30] estimated that about 70% to 80% of ATP in liver is cytosolic and that 90% is unbound. There are as yet no data to question that brain is significantly different, and thus total ATP can be used as a rough approximation of free cytosolic concentration. In contrast to ATP, intracellular ADP and AMP do appear to be significantly bound.[48] Analysis of the equilibria for the reaction catalyzed by cytosolic creatine phosphokinase (see equation 2) can be used to estimate the free ADP concentration if the equilibrium constant and concentrations of ATP, creatine (Cr), PCr, and the pH are known or assumed. Based on such an analysis, Veech et al[45] estimated that free ADP in the normal brain is only 10 to 20 μmol/L, or about an order of magnitude lower than direct chemical measurements. Similar analysis for AMP yields a concentration of 1 nmol/L, a value one to two orders of magnitude lower than chemical assay results.[31]

During the last decade, ^{31}P-nuclear magnetic resonance (NMR) has attracted great attention as a method for the determination of cerebral intracellular concentrations of high-energy phosphate compounds. Advantages of NMR techniques include noninvasive character of the assay and the capability for monitoring changes over time. Present technology, however, has several problems. First, it is rather insensitive, in fact, neither ADP nor AMP can be seen with it and have to be estimated from chemical equilibria or measured chemically. Second, data are derived from ratios of areas under signal curves (e.g., PCr/ATP, PCr/inorganic phosphate, and ATP/inorganic phosphate) and the actual amounts have to be determined by standard analytical methods. Nioka et al[31] published one of the few studies in which direct correlation between NMR and biochemically measured ATP and PCr levels were made. This analysis concluded that, assuming the creatine phosphokinase is at chemical equilibrium (a reasonably well-supported assumption[9]), measurements of PCr, Cr, and ATP by either chemical or ^{31}P-NMR methods allow reasonable estimates of the intracellular levels of these compounds. A summary of chemical and NMR data agree that ATP concentration in the brain is about 3 mmol/L, ADP is 10–20 μmol/L, AMP is 1 nmol/L, and inorganic phosphate is 1.7 mmol/L.

A number of regulatory features of cerebral metabolism come into play to regulate intracellular ATP concentrations. Among these important buffering reactions are those mediated by creatine phosphokinase (CPK):

$$\mathrm{PCr} + \mathrm{ADP} + \mathrm{H}^+ \leftrightarrow \mathrm{ATP} + \mathrm{Cr} \qquad (2)$$

and adenylate kinase:

$$2\mathrm{ADP} \leftrightarrow \mathrm{ATP} + \mathrm{AMP} \qquad (3)$$

The equilibrium constant for the CPK reaction at physiologic Mg^{2+} and H^+ concentrations is about 1.7×10^9, meaning that if PCr is available, any ADP formed will be immediately rephosphorylated. Only after the PCr energy reserve has declined to a very low level will AMP and ADP concentrations increase. This is in fact what has been observed in the brain during threatened energy failure caused by oxygen deprivation, ischemia, seizures, or hypoglycemia. A decrease in PCr precedes that in ATP.[3, 20, 21, 36] Apparently, the concentration of CPK is sufficient for this reaction to be maintained near equilibrium. In neonates, because CPK concentrations are one third to one sixth those in adults, and ATP and PCr decrease together during ischemia,[34] this assumption does not apply. The adenylate kinase reaction (equation 3) is also capable of buffering decreases in ATP.[33]

Adenylate cyclase catalyzes another important reaction involved in the storage and use of high-energy phosphate compounds:

$$2\text{ATP} \leftrightarrow \text{ATP} + \text{AMP} \tag{4}$$

This reaction is most important during conditions of rapid ATP breakdown (e.g., in early ischemia or anoxia), where the increase in the level of AMP is much larger than that of ADP.[20]

Protons are one reactant in the CPK reaction (equation 2). This fact allows intracellular pH to be calculated from knowledge of ATP and PCr concentrations. It also means that hydrolysis of 5 to 6 mmol of PCr to form ATP during threatened energy failure results in consumption of protons equivalent to an alkalinization of the cytosol of about 0.3 pH units, assuming a brain-buffering power of 15 to 20 mmol/pH unit.[29] This alkalinization of the intracellular compartment may be an important metabolic signal: alkalinization causes conversion of glycogen phosphorylase to an active state, and activation of phosphofructokinase to promote increased glycolysis. Thus, during threatened energy failure an initial alkalinization of the cytosol due to consumption of protons in the reaction mediated by CPK (equation 2) may be a metabolic stimulus for increased energy production.

The proton concentration in the intracellular compartment may have an important effect on metabolic machinery and on the injury that results from hypoxia or ischemia. Because protons accumulate when ATP is hydrolyzed, the possibility that increased acidity may be a cause or at least exacerbate the injury has been actively investigated. Studies of brain ischemia and hypoxia indicate that low intracellular pH is associated with adverse metabolic and histologic changes,[22, 42] although whether or not hydrogen ions per se are to blame is controversial.[25] ATP hydrolysis under anaerobic conditions produces protons (see following discussion) that may adversely affect enzyme function and cause impairment of cell volume regulation and disturbance of cell ionic regulation.[42] Low intracellular pH decreases mitochondrial respiration; below pH 6.0 mitochondrial respiration is halted.[14] Other in vitro studies show that low intracellular pH increases free radical formation and lipid peroxidation with severe effects on membrane functions.[2, 42]

Although ATP in the short-term levels can be buffered by the reactions discussed previously, in the longer term catabolism of fuel molecules must provide all of the ATP used for cellular functions. In the adult mammalian brain, ATP cannot long be sustained during anoxia, but in neonates and to an even greater extent in lower vertebrates, ATP levels can be sustained for longer periods.[7, 15] There are several important regulatory processes that are responsible for altering brain metabolic pathways to produce more ATP during hypoxia. One of the most important is the Pasteur effect, which stimulates glucose metabolism with production of lactate. In adults glycolysis can be increased four to fivefold during anoxia, which is insufficient at normal rates of ATP use to prevent energy depletion. It is commonly believed that the process of glycolysis itself generates protons. However, it is fairly clear that the process of glycolysis involves generation of lactate ion without generation of protons. The protons that accumulate during hypoxia and ischemia are largely derived from hydrolysis of ATP. This is evident if lactate production is stimulated under aerobic conditions. Because mitochondrial oxidation is able to maintain a normal ATP pool, no net hydrolysis of ATP occurs, and intracellular pH does not change.[17]

ENERGETIC COSTS OF ION TRANSPORT

ATP generated in the brain is consumed for maintenance of transmembrane electrical and ionic gradients, to supply energy for the biosynthesis, for release and reuptake of neurotransmitters, and for synthesis of neurosecretory compounds. Of these processes, by far the most costly energetically is ion transport. About 70% of the ATP produced in the mammalian brain is consumed in the maintenance of nonequilibrium distributions of ions across cell membranes.[9] Because energy failure appears to be a key feature of anoxia or ischemia, it might be expected that failure of ion transport is an inevitable part of these stresses. Loss of ion regulation during hypoxic or ischemic injuries is significant because failure of ionic homeostasis leads to elevations in intracellular Ca^{2+}, loss of cell volume regulation, and failure of acid–base regulation. Irreversible injury may occur as elevations in intracellular calcium lead to phospholipase activation, release of fatty acids, and membrane damage.[43] During the initial phases of energy failure, the activity of the Na^+-K^+ pump is decreased, and Na^+ accumulates in the cell and K^+ leaks into the extracellular space. Within a few minutes, extracellular $[K^+]$ reaches levels in excess of 20 mmol/L.[12] These events lead to depolarization of neurons and opening of voltage-dependent calcium channels. Ionic and cell volume regulation are lost, as is electrical excitability, synaptic function, and acid–base regulation.

To measure the energy consumed by ion transport or synaptic function, energy consumption must be measured during blockade of ion transport and synaptic function. Michenfelder,[28] using a dog model, studied the cerebral metabolic effects of doses of halothane thiopental sufficient to block synaptic and electrical activity. Astrup et al[1] performed a similar study by infusing lidocaine and ouabain to pentobarbital-anesthetized dogs. In both studies, energy consumption decreased 50% to 60% compared with awake animals. Anesthesia alone (i.e., without these extraordinary measures to reduce synaptic or ion transport activity) reduced metabolism by 20% to 30%. Attempts have also been made to examine these phonemena in isolated CNS tissue to reduce the cardiovascular variability induced by high doses of anesthetics. Treatment with ouabain (a specific blocker of Na^+-K^+ ATPase) or sodium-free solutions[47] or perfusion of unmyelinated nerves in ouabain[37] reduces energy consumption by similar amounts. These results support the idea that ion transport represents the major use of ATP in the brain. It is interesting that the kidneys also show this remarkable dependence of metabolic rate on ion transport.[44] In contrast, the heart uses only 5% to 10% of its total ATP for ion transport. These observations raise an important question: If injury during anoxia or ischemia is in part a consequence of depletion of energy stores, to what extent can reduction of energy consumption during anoxia either prolong the tolerance of anoxic or ischemic conditions or reduce injury during a given insult? Although there is considerable circumstantial evidence to support this concept, we still do not understand all of the physiology involved. By reducing energy used for ion transport, more profound metabolic suppression could be tolerated for cerebral protection. This strategy has been coined "metabolic arrest and ion channel arrest" by Hochachka.[15]

Brain Metabolism in Hypoxia-Tolerant Animals

Important perspectives on cerebral metabolism have been discovered by the study of animals that tolerate far more severe degrees of anoxia or ischemia than adult mammals (for a fascinating review see reference 16). One example of obvious relevance to human medicine are studies showing that prenatal and early neonatal mammals are much more tolerant of hypoxia than adults of the same species.[44] One index of hypoxia tolerance that has been exploited is the depolarization of nerve cell membranes that occur when energy is depleted and ion pumping can no longer sustain transcellular ion and electrical gradients. Hansen[12] found that depolarization of brain cells occurs after 23 minutes of anoxia in neonatal rats and only 2 minutes in adult rats. The most likely explanation of this phenomenon is that ATP conservation due to reduced demands of ion pumping is responsible for conservation of ATP during anoxia. In support of this conclusion is the fact that the neonatal brain has a limited capacity (compared with adults of the same species) to generate ATP anaerobically (i.e., a reduced Pasteur effect[7]), and it is very unlikely that ion pumping cannot continue at normal rates during anoxia because ion pumping consumes such a large fraction of total ATP production. However, in ^{31}P-NMR studies of the neonatal brain during hypoxia, ATP levels are maintained for a considerable period of time.[23] Therefore, maintenance of brain ATP levels, and functions that are dependent on ATP, must be dependent to a great extent on mechanisms that reduce ATP demands, such as decreased ion pumping. It is also reasonable to hypothesize that reduced passive ion permeability may contribute to energy savings.

Hypometabolism may also be critical to the ability of the neonate to withstand hypoxia. Hypometabolism would result in reduced rates of energy use, thereby increasing the temporal tolerance of hypoxia and avoiding the adverse effects of metabolite accumulation. A reduced Pasteur effect in neonates (also exceptionally common in hypoxia tolerant animals[16]) is an example of this strategy of hypometabolism.[7] The net effect is conservation of glycogen and glucose and avoidance of acidosis. In adult brains (e.g., rats) higher brain lactate is generated in response to hypoxia or ischemia despite lower glucose and glycogen levels.[7, 39] An obvious question is whether developmental loss of hypoxia tolerance is due to the acquisition of higher rates of glycolytic metabolism and the adverse metabolic effects of accumulated end products.

Cerebral Protection Via Metabolic Arrest and Ion Channel Arrest

Metabolic arrest strategies rely on the premise that by reducing cerebral energy consumption energy failure will be avoided or at least delayed and ameliorated. A particularly potent example of metabolic arrest is hypothermia. Even mild hypothermia has been shown to produce substantial increases in tolerance of hypoxic or ischemic conditions.[5] Minamisawa et al[27] showed that reduction in brain temperature to 33°C greatly reduced brain injury from ischemia. An interesting finding was that the degree of protection was dependent on the brain region. A proposed mechanism for this protection is that hypothermia may preserve the balance between the rate of membrane based processes that consume ATP (i.e., ion transporters) and the rate of ATP synthesis. Viewed from this framework, cerebral protection might ensue for any pharmacologic intervention that either (1) reduced cerebral metabolic rate, or (2) reduced required ion pumping. One might predict that a combination of cerebral metabolic arrest and ion channel arrest would be a favorable strategy for cerebral protection.

All mammalian cell membranes are quite leaky to ions and thus require a continuous source of energy for maintenance of ionic homeostasis. Quantitatively, by far the most important process is transport of Na^+ and K^+ by the membrane-bound Na^+-K^+ ATPase. This transporter is necessary for maintenance of normal cellular electrical excitability. This transporter moves 3 Na^+

from inside to outside in exchange for 2 K^+ in the opposite direction. In the process 1 ATP is hydrolyzed. The Michaelis constant of the exchanger for Na^+ is about 80 mmol/L; for K^+, about 2 to 3 mmol/L; and for ATP it is about 0.5 mmol/L.[26] This means that under normal intracellular conditions, the presence of elevated intracellular Na^+ is the predominant stimulus for the hydrolysis of ATP by the enzyme.

Calcium is another important ion that requires considerable amounts of ATP energy for its regulation. There are several ATP-requiring mechanisms that are responsible for the maintenance of low intracellular Ca^{2+} concentrations. The plasma membrane Ca^{2+} pump that is present in both the general plasma membrane and especially in synaptic areas is activated by calmodulin and appears to exchange Ca^{2+} for H^+ in a 1:2 ratio.[6] The Michaelis constant of this pump for Ca^{2+} is 0.2 to 0.5 μmol/L and for ATP is 25 to 40 μmol/L; the latter value is 300 μmol/L in the presence of 100 mmol/L Na^+.[10] Energy expenditure for the activity of this pump is about 3% of the total ATP consumption in the cell.[9] Beside the plasma membrane pump, there is also the endoplasmic reticulum Ca^{2+} pump, the mitochondrial Ca^{2+} pump, and the Na^+/Ca^{2+} exchanger fueled by the Na^+ gradient, which is maintained by ATP via the membrane Na^+-K^+ ATPase.

A significant fraction of the ATP energy consumed by membrane ion pumps is spent counteracting passive leak of Na^+ and K^+ ions through large numbers of membrane ion channels. This surprising conclusion seems completely at odds with energy conservation, but the energy spent in the seemingly nonproductive business of continually "bailing out" the cell serves a very important function: heat production. Else and Hulbert[8] point out that ATP hydrolysis by the Na^+-K^+ ATPase is the chief source of metabolic heat and is essentially responsible for mammals' ability to generate heat sufficient for maintenance of a high and constant body temperature. High body temperature in turn permits rapid neural conduction and the remarkable complexity of mammalian neural integration. Thus, it seems possible that the sensitivity of the mammalian brain to hypoxia is one of the compromises made during mammalian evolution, the trade-offs being a highly active brain capable of generating complex behavior, and one inordinately sensitive to oxygen and substrate deprivation. It also raises the possibility, as yet incompletely tested, that "metabolic arrest" combined with "ion channel arrest"[15] may be a valuable strategy to protect hypoxia-sensitive brains.

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CEREBRAL RESUSCITATION, IS IT POSSIBLE?

Leslie Newberg Milde, MD

The purpose of this article is to present the current knowledge of pathophysiology and biochemical changes that occur during and following cerebral ischemia that may contribute to the ultimate neurologic outcome and to present current and future therapeutic measures hypothesized to prevent or ameliorate the secondary insults resulting from cerebral ischemia. This article emphasizes those treatment modalities that may be efficacious when administered during or after ischemia.

ISCHEMIA

Neurologic recovery is not predictable after prolonged ischemia. It is hypothesized that specific biochemical disturbances that occur both during ischemia and after the restoration of circulation contribute to the ultimate neurologic damage.[82] Ischemia results when the decrease in tissue perfusion exceeds the tissue's ability to increase oxygen extraction from the blood.[66] Ischemia consists of inadequate oxygen delivery, inadequate CO_2 removal, increased intracellular lactic acid production, decreased stores of high-energy phosphates (phosphocreatine and ATP), decreased production of ATP, release of excitatory amino acids, and disruption of the blood–brain barrier (BBB).[66, 81] Complete global ischemia occurs with cardiac arrest and results in the cessation of oxidative phosphorylation within 15 to 20 seconds.[1] Anaerobic metabolism with glycolysis supplying ATP continues until the intracellular stores of glucose have been exhausted. Anaerobic glycolysis produces lactic acid, causing a decrease in intracellular pH that peaks a few minutes after the onset of ischemia. When glycolysis ceases and when intracellular ATP concentrations reach zero, all energy-requiring reactions of the neurons cease and they die. Ischemia by

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itself ultimately produces cell death if the duration and severity of the ischemia is sufficient to do so (Fig. 1).

Secondary Consequences of Ischemia

In some clinical situations, a substantial part of the ischemic injury may not have occurred during the period of ischemia but during the period of reperfusion (Fig. 1). The *secondary* consequences of ischemia are those that occur after the cerebral circulation has been restored and may be termed *postischemic injury* or *reperfusion injury*. These include tissue edema, vasospasm, and red cell sludging, all of which can reduce blood flow, causing postischemic hypoperfusion, intracellular acidosis, release of excitatory amino acids, increased catecholamine release, hypermetabolism, secondary depression of previously recovered metabolic activity, intracellular calcium overload initiating calcium-mediated processes, changes in normal chelation and compartmentalization of free metals, and the deregulation of oxygen metabolism, leading to the production of free radicals initiating free radical damage and lipid peroxidation.[18, 56] The gradual development of these processes following ischemia has been termed *maturation*.[58]

Selective Vulnerability

The concept of selective vulnerability applies to the *range* of responses in various regions of the brain that occur in response to the same ischemic insult.

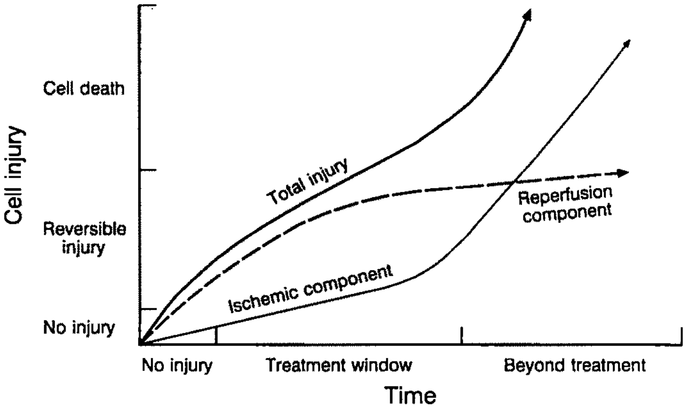

Figure 1. Ischemic/reperfusion injury. Two components of tissue injury contribute to the ultimate neurologic damage. The ischemic component includes the processes of tissue damage occurring during ischemia. Cell death due to the ischemic component alone depends on the severity and duration of ischemia. The secondary consequences of ischemia include the biochemical changes that take place at the time of reperfusion and reoxygenation after ischemia. The duration of these secondary processes and the extent to which they contribute to ultimate neurologic damage will determine the therapeutic window during which treatment administered after ischemia may be effective. (*Modified from* Bulkley GW: Free radical-mediated reperfusion injury: A selective review. Br J Cancer 55(suppl):66, 1987; with permission.)

Certain neurons seem to be more vulnerable to the secondary consequences of ischemia.[61] Regions especially vulnerable to ischemia include the limbic system, especially the pyramidal cells of the CA_1 region of the hippocampus, Purkinje cells of the cerebellum, and small and medium-sized neurons of striatum and layers 3, 5, and 6 of the cortex.[56] Damage to these selectively vulnerable neurons impairs cognition, motor function, coordination, recent memory, emotion, and drive. This accounts for the poor functional neurologic outcome of survivors of cardiac arrest.[28] It is hypothesized that the selective vulnerability of neurons may be due to a combination of specific neuroanatomic connections, synaptic organization, membrane properties, and patterns of neurotransmitters and receptors.[56]

In animal models of ischemia, 2 minutes of cerebral ischemia causes increased spontaneous activity of neurons (hypermetabolism) that persists for 48 hours following reperfusion but results in little or no neuronal death. Five minutes of ischemia causes a biphasic pattern. Decreased neuronal activity soon after reperfusion (1–6 hours) is followed by increased activity (6–72 hours).[18] Five minutes of ischemia produces significant loss of some selectively vulnerable neurons, the pyramidal cells in the CA_1 region of the hippocampus. This death of pyramidal cells is delayed and occurs during the 6 to 72 hours of hypermetabolism. Fifteen minutes of ischemia significantly decreases neuronal activity and 60% of the neurons die. This indicates that 2 to 15 minutes of ischemia can damage selectively vulnerable regions of the brain, while greater than 15 minutes of ischemia can damage all regions of the brain.[61]

This same delay in cell death of selectively vulnerable regions of the brain has also been observed in humans.[76] In patients who died less than 18 hours after cardiopulmonary arrest, there was little damage to the selectively vulnerable regions of the brain, but widespread damage to other brain regions. In those who survived more than 24 hours, there was increased damage in the selectively vulnerable regions. The clinical significance of this observation is the possibility that some regions of the brain may be viable for hours following cardiac arrest and might be amenable to therapeutic interventions administered during this vulnerable period.

Advances in understanding the pathophysiologic mechanisms that mediate cell injury during and after the ischemic insult have led to novel therapeutic approaches to reducing neuronal susceptibility to ischemia. A simple experiment that distinguishes reperfusion injury from primary ischemic injury involves a posttreatment experiment in which a drug expected to block reperfusion injury is given only after the period of ischemia at the onset of reperfusion. If the untreated control subjects exhibit cerebral damage but the postischemic treated subjects do not, the injury must have occurred in the reperfusion period.[8] Drugs presently under investigation for their ability to block reperfusion injury include calcium entry blockers, excitatory amino acid neurotransmitter antagonists, free radical scavengers, antagonists to the arachidonic acid cascade, and agents that block lipid peroxidation of cellular and mitochondrial membranes. In general, the utility of postischemic therapy (resuscitation) for the treatment of tissue injury resulting from ischemia will be related to the proportion of injury that is due to reperfusion versus the proportion due to the ischemia per se.[17] If much of the tissue injury does not take place until the time of resuscitation, then the therapeutic implications could be profound.

CELLULAR PHYSIOLOGY

In order to understand the pathophysiologic changes associated with ischemia and reperfusion, normal cellular physiology is reviewed.

Structure

The cell membrane is a bimolecular phospholipid leaflet. Intercalated in the matrix of this phospholipid bilayer are cholesterol molecules and proteins including the adenosinetriphosphatases (ATPases), adenylate cyclases, and cytochrome oxidases.[93] Other proteins act as receptors to control ion channels. Enzymatic conversion of one phospholipid into another within the cell membrane can alter membrane fluidity, which can influence the opening of ion channels within the membrane. Membrane phospholipid turnover can be stimulated by receptor agonists and neurotransmitters or by calcium ion-activated phospholipase A_2, which degrades phospholipids to lysophospholipids and free fatty acids (FFAs).[93] The high-energy source, ATP, is needed to replenish these membrane phospholipids.

Ion Homeostasis

Sodium and Potassium

Neurons have a voltage-dependent gradient (membrane potential) across their membrane. Energy is expended by neurons to maintain the ion gradients of low intracellular sodium (Na^+), chloride (Cl^-), and calcium (Ca^{2+}) and high intracellular potassium (K^+). There are two major types of ion channels within the cell membranes: voltage-dependent channels and receptor-controlled channels. Changes in membrane potential cause the voltage-dependent channels to open, allowing rapid influx of ions (Na^+ and Ca^{2+}) down their concentration gradient. Other ion-selective channels in the cell membrane are controlled by receptors sensitive to excitatory neurotransmitters. These neurotransmitters can stimulate receptors to open channels that allow Na^+ and Ca^{2+} into the neurons. This net positive flow of charge from the influx of Na^+ and Ca^{2+} into neurons via either voltage-dependent or receptor-controlled channels results in excitation or depolarization. Net negative flow of charge into the neuron results in inhibition or hyperpolarization. The γ-aminobutyric acid opens channels that allow Cl^- to enter neurons, and this negative influx results in inhibition. If, during excitatory synaptic transmission with a positive flow of charge into the cell a critical membrane voltage is reached, the cell will produce a rapidly propagating depolarization, an action potential.

During a nerve action potential, more voltage-dependent channels open in the cell membrane. Na^+ and Ca^{2+} ions will enter the cell because of their chemical gradient and their attraction for the more negatively charged interior of the cell (electrical gradient). Potassium ions, because of their high intracellular concentration, overcome the electrical attraction and move out of the cell. Chloride ions, because of their low intracellular concentration, enter cells despite the negative charge of the interior. No energy is expended by a neuron during depolarization caused by an action potential.

Neurons are constantly working to maintain their resting membrane potential through the action of the energy-dependent pumps. During the recovery phase of the nerve action potential, Na^+ is actively pumped out of the cell and K^+ is pumped into the cell against both their concentration and electrochemical gradients.[91] This is done by a membrane-associated energy-requiring "sodium pump" (Na^+,K^+-ATPase) that maintains the normal Na^+ and K^+ concentration gradients across the cell membrane. The outward transport of Na^+ exceeds the inward K^+ transport, thereby producing the voltage difference across the cell membrane, the inside of the cell being negative relative to the outside (-60 mV). The transmembrane Na^+ gradient established by the sodium pump is necessary not only for the maintenance of ion gradients, but also for the maintenance of cell volume via the regulation of intracellular Na^+, Cl^-, and H_2O, and for the transport of amines, amino acids, and sugars into the cell.[91]

The energy required for the sodium pump is provided by the hydrolysis of ATP to ADP and inorganic phosphate. The ATP for the sodium pump is replenished by the phosphorylation of ADP on the inside surface of the cell membrane. During aerobic metabolism, carbohydrates undergo metabolism to produce ATP via the mitochondrial electron transport system.

Calcium

Regulation of intracellular Ca^{2+} concentration is also essential for normal cell function (Fig. 2). Calcium is necessary for cell excitation and transmitter release; it can inhibit some intracellular enzymes such as the sodium pump and the glycolytic enzymes, and it can stimulate other enzymes either directly or through the action of calmodulin, a calcium-dependent soluble modulator protein.[91]

External free Ca^{2+} concentration is approximately 10^{-3} mol/L, with total intracellular Ca^{2+} concentration being the same. However, 10^{-4} Ca^{2+} within the cell is stored on internal membranes within the endoplasmic reticulum and mitochondria. The resulting intracellular free Ca^{2+} concentration gradient is therefore 10^{-7} mol/L. This results in a free Ca^{2+} concentration gradient of 10,000 to 1 between the extracellular fluid and the cytosol.[91, 93] This large gradient causes Ca^{2+} to enter the cell. Calcium ions enter the cell through three mechanisms (Fig. 2): (1) Ca^{2+} may enter through the voltage-dependent chan-

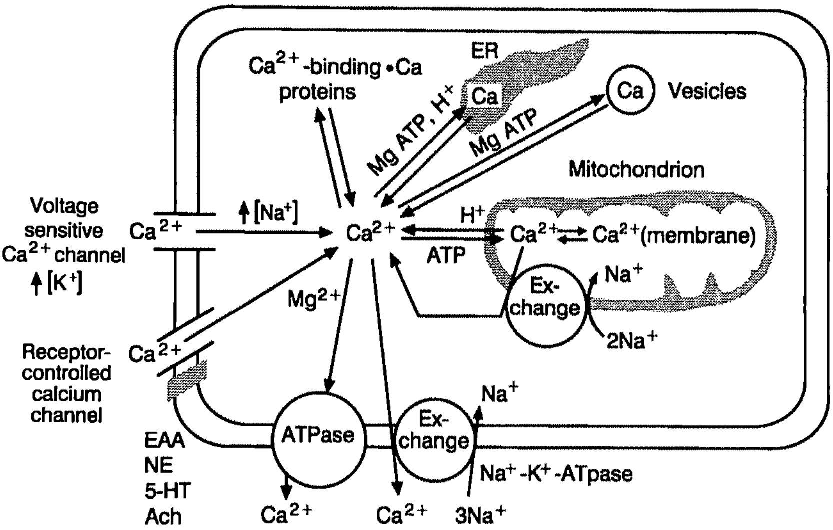

Figure 2. Calcium transport processes. Calcium influx through cell membranes is passive down a concentration gradient through voltage-sensitive and NMDA receptor-controlled Ca^{2+} channels. Calcium efflux is through a Ca^{2+} translocase and an Na^+/Ca^{2+} exchange mechanism, both of which require energy. Calcium uptake into cellular organelles (endoplasmic reticulum, vesicles, mitochondria) requires energy. (*Modified from* Milde LN: Pathophysiology of ischemic brain injury. Crit Care Clin 5:729, 1989; with permission.)

nels. These channels are activated by an increase in extracellular K^+ or an increase in intracellular Na^+. (2) Calcium may enter when an agonist such as one of the excitatory amino acid neurotransmitters (glutamate or aspartate), norepinephrine, acetylcholine, or 5-hydroxytryptamine, bind to a membrane receptor to open receptor-controlled calcium channels.[93] (3) Calcium may also enter when changes in membrane fluidity occur via conformational changes in the protein structure within the cell membrane.

The high concentration gradient of Ca^{2+} across the plasma membrane is maintained by the active removal of Ca^{2+} from the cytosol. There are four energy-dependent Ca^{2+} transport systems (Fig. 2). There are two Ca^{2+} ion pumps in the plasma membrane. One is an ATP and magnesium-dependent Ca^{2+} -ATPase translocase containing calmodulin, which pumps Ca^{2+} out of the cell. The capacity of this pump is relatively small. Most Ca^{2+} efflux occurs through a Ca^{2+} /Na^+ exchange mechanism in which three Na^+ ions are exchanged for one Ca^{2+} ion. The energy for this Ca^{2+} -Na^+ exchange is provided by the normal inward movement of Na^+ down its concentration gradient.[91] During periods of intense synaptic activity, the increase in intracellular Na^+ decreases the transmembrane Na^+ concentration gradient and results in less efficient Ca^{2+} efflux.[21] A third Ca^{2+} transport system moves Ca^{2+} into the endoplasmic reticulum facilitated by a transmembrane hydrogen ion (H^+) gradient. This transport system also requires energy from ATP.[91] Only when the intracellular Ca^{2+} concentration is increased despite the other three removal mechanisms does the fourth transport mechanism become operative. Mitochondria are capable of removing excess Ca^{2+} from the cytosol. In mitochondrial membranes, Ca^{2+} is exchanged for H^+ using energy obtained from mitochondrial respiration. Because this uncouples oxygen consumption from phosphorylation, the amount of ATP normally synthesized by the mitochondria is decreased. Calcium ion release from the mitochondria occurs via a Ca^{2+} -Na^+ exchange mechanism.[91] In summary, Ca^{2+} influx into the cell across the cell membrane and Ca^{2+} release from the mitochondria are spontaneous processes, whereas the active transport of Ca^{2+} out of the cell and sequestration of Ca^{2+} by the mitochondria require energy in the form of ATP.

PATHOPHYSIOLOGY OF ISCHEMIA

Vascular Changes

The major vascular change following cerebral ischemia is delayed postischemic hypoperfusion.[6, 56] When the circulation is restored following complete global ischemia there is a 15- to 20-minute period of reactive hyperemia. This occurs because the viscosity of the blood washing through the microcirculation is decreased relative to that of the stagnant blood pooling in the vascular beds[56] and because vascular tone is temporarily decreased by vasoactive substances elaborated during ischemia. Following this reactive hyperemia, postischemic hypoperfusion develops. The severity and duration of the postischemic hypoperfusion depends on the severity and duration of the ischemic insult. There is limited evidence that this postischemic hypoperfusion contributes to the ultimate neurologic damage occurring after ischemia,[57, 74] and that postischemic hypoperfusion in areas of increased functional (and metabolic) activity may contribute to the selective vulnerability of neurons in that area.

This postischemic hypoperfusion may be due to vasoconstriction caused by Ca^{2+} activation of the contractile mechanisms in endothelial cells. An increase in intracellular Ca^{2+} in vascular smooth muscle cells occurring during ischemia activates myosin light-chain kinase, which in turn catalyzes the phosphorylation of myosin. This increases the actin-myosin interaction, resulting in contraction.[113] An increased production of thromboxane A_2, a potent vasoconstrictor made from arachidonic acid during the recirculation and reoxygenation period following ischemia, may also contribute to the hypoperfusion. This hypoperfusion cannot be influenced by sympathomimetic vasoconstrictors or sympatholytic, direct-acting, or ganglionic blocking vasodilators, but can be ameliorated by some calcium entry blockers and inhibitors of prostaglandin synthesis (see following).

Membrane Changes

With complete cerebral ischemia the high-energy phosphate stores of phosphocreatine are depleted within 1 minute; glucose and glycogen stores, within 4 minutes; and ATP stores, within 5 to 7 minutes.[93] This exhaustion of energy stores leads to failure of the sodium pumps, allowing further influx of Na^+ and Cl^-, efflux of K^+, and membrane depolarization.[53, 81, 93] The influx of Na^+ and Cl^- is accompanied by H_2O, which produces cell swelling.[93] When the extracellular K^+ concentration increases, changes in the plasma membrane potential open voltage-dependent Ca^{2+} channels and increased concentrations of extracellular glutamate open receptor-controlled channels (see section on Excitatory Amino Acid Neurotransmitters), resulting in a massive intracellular influx of Ca^{2+}.[11, 53, 81, 93] It is assumed that this failure of membranes to maintain normal ion gradients characterizes irreversible cell injury.

Mitochondria

Mitochondrial dysfunction also characterizes irreversible cell injury. The primary factors believed to cause cerebral mitochondrial damage during ischemia include intracellular lactic acidosis, Ca^{2+}-activated degradative enzymes, mitochondrial Ca^{2+} overload, and free radical–induced membrane lipid peroxidation. Intracellular acidosis inhibits both mitochondrial respiration and Ca^{2+} sequestration by the mitochondria.[51, 55] Calcium-activated degradative enzymes including phospholipases and proteases destroy phospholipids and proteins within cell and mitochondrial membranes. Mitochondrial sequestration of Ca^{2+} damages the mitochondrial electron transport chain and the synthesis of ATP.

Calcium

During ischemia Ca^{2+} enters the cells through both voltage-dependent and agonist-receptor–controlled channels and accumulates in the cytosol. This intracellular Ca^{2+} overload appears to be one of the common pathways leading to irreversible cell damage and death (Fig. 3). Calcium influx activates proteases that destroy cell membranes, resulting in receptor dysfunction and the failure of intracellular transport mechanisms. Increased intracellular Ca^{2+} also activates phospholipases A_1, A_2, and C, which hydrolyze phospholipids within mitochondrial and cell membranes to physically disrupt these membranes. These enzymes do not require oxygen or energy and so may function during or after ischemia. Hydrolysis of the membrane phospholipids release FFAs, which have

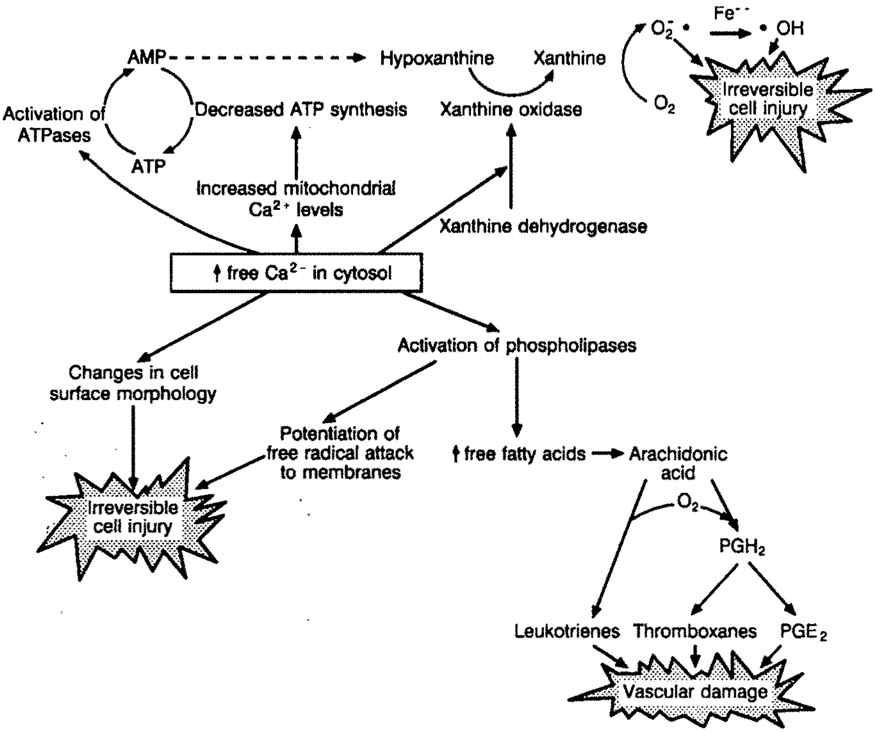

Figure 3. Relationship between energy supply, cellular calcium regulation, the arachidonic acid cascade, the formation of prostaglandins, and the formation of free radicals. During ischemia, cellular stores of ATP are metabolized to AMP and ultimately to hypoxanthine. Increased cellular concentrations of Ca^{2+} activate proteases converting xanthine dehydrogenase to xanthine oxidase, which catalyzes the metabolism of hypoxanthine to xanthine with superoxide radicals ($O_2^{-\bullet}$) as a byproduct. Increased intracellular Ca^{2+} also activates phospholipases to release free fatty acids from cell membranes. During the reperfusion period with the presence of oxygen, arachidonic acid is metabolized to prostaglandins and leukotrienes. Free radicals and prostaglandins are responsible for cell injury following ischemia. (*Modified from* Fuller BJ, Gower JD, Green CJ: Free radical damage and organ preservation: Fact or fiction? Cryobiology 25:377, 1988; with permission.)

detergent properties that can destroy the lipid portions of all membranes. The major FFA is arachidonic acid, which can be metabolized to free radicals, prostaglandins, and leukotrienes,[81, 116] which can produce further changes in membrane permeability and ion distribution.[53, 81] The normal mechanisms for control of intracellular Ca^{2+} concentration include the cell membrane ATP-dependent Ca^{2+} translocase, the cell membrane Ca^{2+}/Na^{+} exchange pump, the ATP-dependent Ca^{2+} uptake of Ca^{2+} into the endoplasmic reticulum, and the sequestration of Ca^{2+} by the mitochondria at the expense of oxidative phosphorylation.[93] All require energy and will consume any ATP reserves. Only mitochondrial sequestration is available to the ischemic cell.

Calcium Entry Blockers

The calcium entry blockers form a heterogenous group of drugs, including derivatives of papaverine, dihydropyridine, and piperazine. These drugs block the influx of Ca^{2+} through the voltage-sensitive ion channels into the cells[112] and can block intracellular flux of calcium into mitochondria.[4, 94] They are structurally and operationally distinct from the antagonists of excitatory neurotransmitters, which also block the entry of Ca^{2+} into the cell but through the excitatory amino acid neurotransmitter receptor–controlled ion channel.

The calcium entry blockers vary in their effects on the myocardium and the vasculature. The source of calcium necessary for contraction of cerebral arteries is primarily from the extracellular space. This is unlike systemic arteries, which use a bound intracellular pool of calcium for contraction.[108] This makes the cerebral vessels especially vulnerable to those calcium entry blockers that primarily block influx of calcium into cells. The calcium entry blockers that have been studied for brain protection were chosen because of their effect on cerebral vessels in vitro. These include lidoflazine, nimodipine, and nicardipine. Protection by these agents has been studied in focal ischemia and in complete global ischemia secondary to cardiac arrest.

Lidoflazine

Lidoflazine has been investigated only for its use in the prevention of neurologic damage from complete global ischemia following cardiac arrest. In animal models of cardiac arrest, the results with lidoflazine have been contradictory. One study reported improvement in postischemic hypoperfusion,[117] while subsequent studies have failed to demonstrate any effect of lidoflazine on postischemic cerebral blood flow.[33, 121] Two animal studies have reported improvement in neurologic outcome with lidoflazine following complete cerebral ischemia,[110, 121] while three studies have failed to demonstrate any improvement in neurologic outcome.[33, 34, 109] The only randomized *clinical* trial studied lidoflazine administered to patients remaining comatose following resuscitation from cardiac arrest. Lidoflazine produced no improvement in the proportion of patients who died, in the proportion who survived with good neurologic function, or in the proportion who survived with poor neurologic function.[15] From this it can be concluded that lidoflazine, by itself, has no effect in ameliorating neurologic damage that occurs following prolonged cardiac arrest. Whether the neurologic damage was a result of prolonged ischemia itself, which lidoflazine, administered after the event, would not be expected to affect, or a result of injury occurring in the recirculation period, the time when lidoflazine might have had some therapeutic efficacy, is unknown.

Nimodipine

Nimodipine, a dihydropyridine derivative, is the calcium entry blocker most extensively studied for its protective effects against cerebral ischemia. It has been studied in animal models of focal ischemia and in patients with acute strokes or following subarachnoid hemorrhage. It has also been studied in animal models of complete cerebral ischemia and in patients surviving cardiac arrest. Studies of the effect of nimodipine on regional cerebral blood flow (rCBF) when treatment is begun following the onset of focal ischemia are contradictory. Two report improvement in rCBF to the ischemic areas accompanied by a decrease in infarct size and an improvement in neurologic recovery.[44, 67] However, one study reported that treatment with nimodipine after the ischemic event failed to modify the pattern of rCBF distribution and had no effect on infarct size.[45]

In a study of patients with acute stroke, nimodipine produced a significant improvement in rCBF to the ischemic hemisphere, indicating that nimodipine produced an inverse (or Robin Hood) steal.[41] In two randomized, blinded, placebo-controlled trials of patients with acute strokes, treatment with nimodipine orally (120 mg daily) for 1 month following the stroke resulted in significantly less mortality and significantly faster and better improvement in neurologic function.[42, 43] However, nimodipine had a differential effect on recovery. Neurologic recovery was greater in those patients whose initial deficits were mild to moderate. If the initial deficits were severe, nimodipine produced no improvement.[43] These studies on rCBF and neurologic outcome suggest that improvement in neurologic function is correlated with improvement in rCBF to the ischemic area and its penumbra. If the ischemia is so severe that rCBF is below the threshold for maintenance of cellular integrity, irreversible cell damage occurs and there is no improvement in rCBF by nimodipine. Nevertheless, these clinical trials are promising and suggest that nimodipine may be of benefit if started within 24 hours of the onset of stroke and administered in addition to standard treatment.

Nimodipine has been most extensively studied for its role in the treatment of vasospasm following subarachnoid hemorrhage. Several prospective randomized, blinded, placebo-controlled studies on the use of nimodipine in patients following subarachnoid hemorrhage[5, 71, 72, 77–79] reported that patients treated with nimodipine had a significantly lower incidence of delayed ischemic deficits or death or had significantly better neurologic outcome than those patients given placebo. While the number of patients in each of these studies was small, a meta-analysis of these studies demonstrated clearly that nimodipine treatment administered following subarachnoid hemorrhage significantly decreased the incidence of delayed ischemic defects, although there was no demonstrable difference in the extent and severity of vasospasm as determined by cerebral angiography.[83] Similar to its effects in patients following stroke, nimodipine seemed to produce the most improvement in patients with moderately severe symptoms and produced little or no improvement in patients with severe symptoms.[77] The mechanism(s) of action of nimodipine in the amelioration of neurologic damage following subarachnoid hemorrhage remain unclear. Nimodipine may be affecting the vasculature but does not seem to prevent vasospasm (at least as determined grossly by angiography), although it may lessen the severity of the vasospasm. However, it may be acting through its effects on neurons by preventing Ca^{2+} entry into the cells, Ca^{2+} sequestration by mitochondria, and the subsequent alterations in FFA metabolism and the arachidonic acid cascade.

Nimodipine has also been studied for a possible protective effect in complete cerebral ischemia. It has been reported that treatment with nimodipine administered after complete cerebral ischemia significantly ameliorated postischemic hypoperfusion.[60, 69, 104] This flow enhancement by nimodipine is regionally heterogeneous, but tends to redistribute blood flow such that areas of low flow receive a greater increase in rCBF than areas of high flow, another example of a Robin Hood steal.[99] Treatment with nimodipine after[102] ischemia has also been shown to significantly improve neurologic recovery. Because nimodipine improved both postischemic hypoperfusion and neurologic outcome, it has been concluded that postischemic hypoperfusion does contribute to the ultimate neurologic damage occurring after complete global ischemia. A prospective, randomized, blinded placebo-controlled clinical trial of low-dose nimodipine in a small number of patients following cardiac arrest demonstrated that nimodipine significantly improved postischemic cerebral blood flow and shortened the time to awaken from coma but did not improve ultimate neurologic outcome.[37] A larger prospective randomized placebo-controlled study of patients resuscitated from cardiac arrest reported that there was no improvement in survival rate or neurologic function in those patients receiving nimodipine. However, in a subset of patients in whom advanced life support measures were delayed 10 minutes or more from the onset of cardiac arrest, treatment with nimodipine significantly improved survival rate.[84, 85]

It has also recently been reported that another dihydropyridine derivative, nicardipine, significantly improved the postischemic hypoperfusion following complete global ischemia but failed to improve neurologic outcome,[89] thus confusing the issue as to whether the postischemic hypoperfusion does contribute to ultimate neurologic damage.

These results suggest that calcium entry blockers may be able to provide limited protection of, or improvement in, neurologic function when given following cerebral ischemia. Whether the major mechanism(s) of action for this protection is an effect on the cerebral vasculature causing improvement in or redistribution of cerebral blood flow or whether it is due to other subcellular neuronal effects has yet to be determined. The results do confirm the hypothesis that events occurring during the restoration of circulation following ischemia do contribute to the ultimate neurologic damage. This provides the impetus for further studies to elucidate the mechanism(s) of action of these or other calcium entry blockers in the postischemic period.

Excitatory Amino Acid Neurotransmitters

The dicarboxylic amino acids, glutamate and aspartate, are excitatory neurotransmitters in many brain regions.[22, 64] Glutamate is normally stored in vesicles in presynaptic terminals of neurons and released when the presynaptic axon is depolarized by calcium influx. Glutamate then acts at receptors on the postsynaptic neuron.[24, 36] Normally, the *extracellular* concentrations of glutamate increase only very briefly during synaptic transmission because of energy-requiring reuptake mechanisms in nerve terminals[106] and glia.[54] During cerebral ischemia, there is increased synaptic release[31] and impaired cellular reuptake of glutamate,[31] resulting in a rapid increase of extracellular glutamate.[24, 95] This increased extracellular concentration of glutamate then becomes neurotoxic.

There are primarily three postsynaptic receptors for the excitatory neurotransmitters, the *N*-methyl-D-aspartate (NMDA) receptor, the quisqualate (α-amino-3-hydroxy-5-methyl-4-isoxazole [AMPA]) receptor, and the kainate receptor.[9] NMDA receptors occur in layers 3, 5, and 6 of the cerebral cortex, thalamus, striatum, Purkinje, and granule cell layers of the cerebellum, and the CA_1 region of the hippocampus. There are high concentrations of this receptor in those brain regions that show selective vulnerability to ischemia. AMPA receptors occur in deep layers of cerebral cortex, thalamus, the striatum, the molecular layer of the cerebellum, and the pyramidal cell layer and striatum lucidum of the hippocampus. Kainate receptors have been found only in the striatum lucidum of the hippocampus. Glutamate acts on all three receptor while aspartate acts only on the NMDA receptor. All three receptors are linked to membrane cation channels. The kainate and quisqualate receptors are linked to membrane channels that allow the inlux of Na^+.[22]

To date, most research has focused on the NMDA receptor-controlled ion channel complex (Fig. 4). The NMDA receptor is coupled to a membrane channel permeable to either Na^+ or Ca^{2+} influx, which can be blocked by magnesium (Mg^{2+}) attached to receptors within the channel. It is theorized that Mg^{2+} ions retain water, and in this bulky state block the NMDA channel.[9] Zinc (Zn^+) can act as an antagonist of Mg^{2+} by attaching to its binding sites within the ion channel. There are three major sites where pharmacologic agents can antagonize the NMDA receptor-channel complex (Fig. 4).[3] These are the glutamate receptor binding site, the NMDA associated ion channel binding site, and the glycine binding site. Both chemical and electric signals affect the activity of the NMDA receptor-channel complex. Glutamate and aspartate excite the NMDA receptor. Glycine, usually an inhibitory transmitter, binds at a different site on the NMDA receptor to allow activation by glutamate. If glycine is not present, the normal concentrations of glutamate will not open the NMDA receptor–controlled ion channels. The electrical potential associated with the neuronal membrane also regulates NMDA receptor and its ion channel activity. At a normal resting membrane potential the NMDA ion channel is closed and an agonist at the receptor will induce little ion flux. Depolarization excites the NMDA receptor and dislodges the Mg^{2+} ions that block the NMDA channel when the cell is at rest. Activation of the NMDA receptor opens the ion channel, allowing influx of Na^+ and Ca^{2+} into the neuron. Persistent stimulation of the NMDA receptor causes these ion channels to be held open, with a resultant intracellular accumulation of Na^+, which causes osmotic swelling and cell death, and Ca^{2+}, which initiates a cascade of events that may lead to cell death.[23]

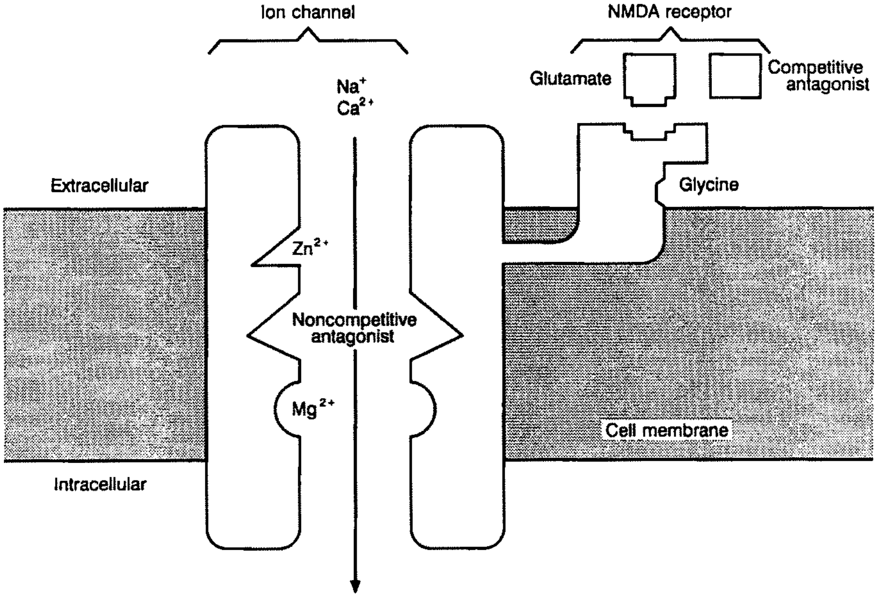

Figure 4. Speculative schematic diagram of the NMDA receptor–controlled ion channel complex. Glutamate binding is facilitated by glycine and antagonized by competitive antagonists. Magnesium (Mg^{2+}), zinc (Zn^{2+}), and noncompetitive antagonists block the ion channel at specific binding sites. (*Modified from* Albers GW: Potential therapeutic uses of N-methyl-D-aspartate antagonists in cerebral ischemia. Clin Neuropharmacol 13:177, 1990; with permission.)

Under certain pathologic conditions, including ischemia, glutamate can become a neurotoxin. The toxic changes produced by glutamate are of two types: immediate injury and delayed neuronal death. Immediate neuronal injury occurs following severe ischemia with energy depletion and is due to acute cell swelling. This depends on the presence of extracellular Na^+ and Cl^- Opening the membrane ion channels allows an influx of Na^+, membrane depolarization, a secondary passive influx of Cl^- and with it, water, to produce cell swelling.[20, 73, 87] The cell swelling eventually causes lysis of the cell membrane and death.[87]

There is also a more slowly evolving neuronal degeneration in which neuronal injury may not be apparent for up to 24 hours. While Ca^{2+} can enter the cell through several routes: voltage-sensitive channels activated by membrane depolarization, nonspecific leak conductance associated with cell swelling, or reverse operation of the Na^+-Ca^{2+} exchange mechanism, the membrane channels controlled by NMDA receptors appear to be the most important for glutamate-related injury, i.e., involving the selectively vulnerable regions of the brain.[70] The NMDA receptor–controlled channel may allow the highest percentage of calcium influx of any Ca^{2+} channel. It is theorized that the resultant increase in intracellular Ca^{2+} starts a cascade of reactions ultimately responsible for neuronal degeneration (see section on Calcium). Calcium entry into neuronal postsynaptic terminals can also increase the release of glutamate, thereby further propagating injury via a positive feedback loop. This late propagation, in conjunction with the intrinsically delayed nature of the calcium-dependent glutamate injury, may account for the fact that ischemic neurologic injury can require 24 to 72 hours to fully develop.[61, 76, 80]

Glutamate has been implicated as a mediator of neuronal damage during ischemia by the following information.[27] (1) The distribution of excitatory neurotransmitter receptors occurs primarily in those areas of the brain that are considered to be selectively vulnerable to ischemia. (2) Ischemia is associated with an increased concentration of glutamate in the extracellular space within a few minutes after cessation of blood flow.[10] (3) There is increased neuronal firing in the hippocampus produced by excitatory amino acids for up to 24 hours following even 5 minutes of ischemia.[107] (4) The interruption of glutaminergic nerve tracts to areas of high concentration of glutamate receptors has been reported to protect against ischemic injury.[119] (5) High concentrations of Mg^{2+}, which block synaptic transmission in general and NMDA receptor-controlled ion channels specifically, decrease ischemic neuronal injury.[59, 86] (6) Pharmacologic blockade of postsynaptic NMDA receptors attenuates ischemic neuronal injury.[23] (7) In the first few minutes of reperfusion Ca^{2+} accumulates in neurons in a nonselective pattern, presumably due to entry through the voltage-dependent channels and impaired outward pumping of calcium. When energy metabolism is restored, the less vulnerable neurons rapidly return to normal appearance whereas the CA_1 and CA_3 pyramidal neurons show continuing accumulation of Ca^{2+} with excitotoxic changes.[97] This is likely a consequence of burst firing brought about through the activation of NMDA receptors and Ca^{2+} influx through the NMDA receptor-controlled channels.[65]

There are several types of antagonists to the NMDA receptor-ion channel complex. The action of glutamate can be antagonized *competitively* by compounds that compete for the glutamate receptor binding site. Competitive antagonists are highly polar molecules with poor BBB penetration. Synthesized competitive antagonists that do cross the BBB and therefore can act following systemic administration include the competitive antagonists CGS 19755, CPP, AP-7, CGP 37849, CGP 39551, and NPC 12626. However, because of the difficulty in making a nontoxic competitive antagonist with adequate BBB penetration that is effective in low concentrations, most biochemical research has concentrated on the noncompetitive antagonists.

The action of glutamate can also be antagonized *noncompetitively* by compounds that bind within the ion channel, thereby impeding ion flux through the channel. These include Mg^{2+}, Zn^{+} or other compounds that bind to a separate phencyclidine site within the channel. These include dizocilipine maleate (MK-801) and the dissociative anesthetics ketamine and phencyclidine, which block the NMDA receptor–associated ion channel in the open state, and dextorphan and dextromethorphan, which block the ion channel in the closed state.[22] These noncompetitive antagonists are lipid soluble, easily cross the BBB, tend to concentrate in the brain, and have short and predictable half-lives. The effect of the noncompetitive antagonists is not likely to be overcome by increasing levels of glutamate, which could displace the competitive antagonists. Potential side effects of the noncompetitive NMDA antagonists include non–NMDA-mediated excitatory synaptic transmission, impairment of learning,[26] morphologic neuronal changes, and psychomimetic and adverse behavioral properties.[2, 88]

Antagonists can also block glycine-binding site. These include HA-966, chlorokynurenate, ACBC, and $12CA^2$, which have been shown to prevent neuronal injury following ischemia.[52, 75] Agents that interfere with the secondary effects of excessive NMDA activation or inhibit glutamate release during ischemia are also being investigated. In the future, these compounds might prove advantageous because they do not interfere with normal NMDA-mediated neuronal transmission.

Several studies have been done with NMDA receptor antagonists to suppress excitatory transmission following ischemia to determine the effect on neurologic outcome. However, the results have been conflicting.[68, 98] Improved outcome has been reported when NMDA antagonists were given after the onset of ischemia.[23, 38, 63, 96, 105] Many of these reported improvements were based only on histologic changes emphasizing areas of known NMDA receptor concentration, the selectively vulnerable areas. However, the studies on the effects of NMDA antagonists in global ischemia have produced mixed results.[2] In some studies reporting improvement following complete ischemia, the noncompetitive receptor antagonist, MK-801, was given. This drug is known to decrease body temperature if not aggressively maintained so that decreases in brain temperature could have provided the observed neurologic protection rather than MK-801. Postischemic treatment with MK-801 has not been shown to be effective following global ischemia in rats[118] although posttreatment has been effective following global ischemia in gerbils.[12, 13] It may be that the density of the ischemic insult may determine the efficacy of NMDA receptor antagonists.

Recent investigation has centered on the quisqualate or AMPA receptor-controlled ion channel complex. AMPA receptors mediate rapid excitatory transmission in the brain. AMPA receptor activation causes depolarization of the plasma membrane, allowing Na^+ and K^+ influx. AMPA receptor stimulation may activate voltage-dependent ion channels and may reverse the 3 Na^+/Ca^{2+} exchange mechanism. It has been demonstrated that an antagonist to the AMPA receptor (NBQX) readily crosses the BBB and can decrease ischemic neuronal injury even when administered following ischemia. The exact intracellular mechanisms whereby AMPA receptor activation contributes to cell injury is unknown. However, blockade of this receptor may become an important therapeutic intervention against brain damage from cerebral ischemia in the future.

The previously mentioned studies suggest that neuronal damage secondary to an excitotoxic insult may not simply be the result of damage occurring at the time of ischemia, but may be at least partially mediated by events occurring after ischemia. Later, neurotoxicity by glutamate may be due to the leakage of glutamate from damaged neurons or from increased synaptic glutamate release secondary to increased intracellular calcium occurring as a result of the ischemia.[2] This could explain the delayed histologic appearance of ischemic neuronal injury that has been observed.[76] This late propagation of ischemic damage may underlie the therapeutic successes reported when NMDA antagonists are administered after the ischemic event.

Present evidence suggests that selective neuronal death after transient cerebral ischemia does involve an excitatory action of neurotransmitters. NMDA or AMPA antagonists may offer a new strategy for the treatment of ischemic brain injury. This new approach is supported by a scientific foundation and some promising results with therapy in a variety of animal models of ischemia. The identification of several different classes of drugs that can block excitation at postsynaptic receptors opens the possibility for prevention and treatment for cerebral ischemia. Further studies should identify active compounds and their possible use in preventing or ameliorating the neurologic damage produced by ischemia. Additional studies will determine whether the protective effect of these agents in the experimental setting can be applied to the clinical situations to provide protection from neurologic injury *after* an ischemic insult has occurred.

Prostaglandins

Prostaglandins are products of the interaction between molecular oxygen and FFAs (Fig. 5). Accessible phospholipids from cell membranes are converted by hydrolysis to FFAs by phospholipase A_2. Phospholipase A_2 is activated by a surface stimulus or by an influx of Ca^{2+} into the cell as occurs during ischemia. FFAs are normally converted to acyl-CoA by an ATP-dependent ligase. How-

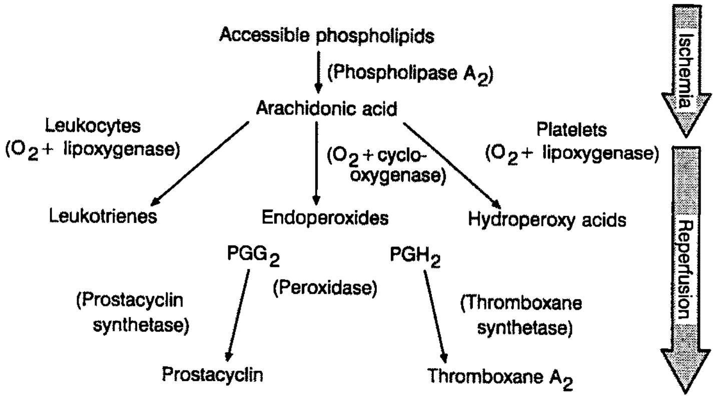

Figure 5. Role of arachidonic acid in the production of leukotrienes, endoperoxides, hydroperoxy acids, and prostaglandins, with reperfusion and reoxygenation after ischemia. (*From* Milde LN: Pathophysiology of ischemic brain injury. Crit Care Clin 5:729, 1989; with permission.)

ever, during ischemia this conversion to acyl-CoA cannot take place because of the depletion of ATP. Therefore, the concentration of FFAs increases. High concentrations of FFAs can be deleterious to mitochondrial function because they uncouple oxidative phosphorylation, cause efflux into the cytosol of K^+ and Ca^{2+} ions stored in the mitochondria, produce cerebral edema, and increase prostaglandin synthesis.

The most common FFA is arachidonic acid, the precursor of the prostaglandins. The concentration of arachidonic acid in normal tissues is near zero. The hydrolysis of membrane phospholipids to arachidonic acid through the activation of phospholipase A_2 is the initial step in the production of prostaglandins.[122] An increase in arachidonic acid concentration can be stimulated by a variety of conditions, including trauma, hypoxia, severe hypoglycemia, pyrogen fever, convulsions, tissue dissection, or ischemia.[122] With reperfusion and reoxygenation following ischemia, arachidonic acid is converted by cyclo-oxygenase to the endoperoxides PGG_2 and PGH_2, which are short-lived intermediates (Fig. 5). PGG_2 is the precursor of prostacyclin (PGI_2) made in vascular endothelial cells, while PGH_2 is the precursor of thromboxane A_2 (TxA_2) synthesized in platelets. Arachidonic acid is also converted by lipoxygenase in leukocytes to leukotrienes, which are the slow reactive substances of anaphylaxis (SRS-A) and by lipoxygenase in platelets to hydroperoxy acids (HPETE) and peroxy acids (HETE).[120] It is hypothesized that during and immediately following ischemia the endoperoxide intermediates tend to inactivate prostacyclin synthetase, which is in the wall of the ischemic cerebral vessels so that relatively less prostacyclin (a potent vasodilator) is made.[32] The reduced synthesis of prostacyclin then results in increased synthesis of thromboxane A_2,[111] a potent vasoconstrictor, which may contribute to postischemic hypoperfusion.

Arachidonic acid itself, the short-lived endoperoxides, and thromboxane A_2 are potent platelet aggregators that can contribute to hypoperfusion. The endoperoxides are also potential free radicals and an increase in their production may elicit a cascade of harmful reactions including cross-linking reactions of membrane phospholipids and proteins and peroxidation of the polyunsaturated fatty acids in cell membranes. These reactions have the potential to irreversibly change cell structure such that cell and mitochondrial membrane function is altered (see section on Free Radicals).

It has been hypothesized that inhibitors of the arachidonic acid cascade might attenuate postischemic hypoperfusion and thereby ameliorate neuronal damage following ischemia. The production of prostaglandins can be blocked by the cyclo-oxygenase inhibitor, indomethacin, if given before the ischemic event.[30] However, inhibition of prostaglandin synthesis by indomethacin given after ischemia has no effect on postischemic hyperperfusion or on neurologic outcome.[14, 49] It has therefore yet to be shown that the administration of inhibitors of prostaglandin synthesis can resuscitate the brain, i.e., be efficacious when given after the ischemic event.

Free Radicals

Most molecules have chemical bonds consisting of a pair of electrons. The two electrons spin in opposite directions, thereby canceling each other's magnetic field, resulting in a low energy state. Free radicals are molecules with an odd number of electrons formed by a break in a covalent bond. The bond splits symmetrically and both fragments of the molecule retain a single electron. This unpaired electron has a magnetic field that produces a high energy state, making the molecule highly reactive and unstable, with a very short half-life.[103] Because of this, free radicals exist only in very low concentration and do not travel far from their site of formation. Such molecules react with adjacent nonradical molecules to produce a stable molecule and a new free radical. This starts a chain reaction of free radical generation. Each free radical in turn can react with another molecule and so on until the chain reaction is terminated by the random collision of two free radicals to form a molecule with a stable bond or until a scavenger molecule is met.

Free radicals are produced in small amounts in normal cellular processes.[90] Free radicals are normally generated during oxidative phosphorylation in the mitochondrial electron transport system in which production of ATP is linked to the reduction of molecular oxygen to water.[25] Under normal conditions the mitochondrial electron transport system adds four electrons at once to O_2, reducing it to H_2O. However, leaks in the mitochondrial electron transport allow the acceptance of single electrons. If the four electrons are acquired singly, a series of free radical intermediates are formed (superoxide, $O_2^{\bullet}$; hydrogen peroxide, H_2O_2; and the hydroxyl radical, $^{\bullet}OH$).[25] These free radicals usually remain tightly bound within the mitochondrial membrane so that they can donate electrons further down the mitochondrial electron transport system. Normally they present no threat to the cell. Some leak of the free radicals does occur, but this is usually controlled by scavenging mechanisms. Free radicals can also be produced in reactions catalyzed by prostaglandin hydroperoxidase, by auto-oxidation of small molecules including the catecholamines, and by the microsomal cytochrome P-450 reductase system.[39]

Superoxide is the first free radical formed by the univalent reduction (adding one electron) to molecular oxygen. Under normal conditions, superoxide radicals dismutate slowly to hydrogen peroxide.[40] This same step can occur rapidly when catalyzed by the superoxide dismutase enzymes. Superoxide dismutases are protective enzymes that efficiently and specifically scavenge the superoxide radical by catalyzing its dismutation to hydrogen peroxide and oxygen. These scavenging enzymes are primarily inside the cell. Superoxide can leave the cell through the cell membrane anion channels. Superoxide radicals may then spread damage beyond the original site of radical formation.

Hydrogen peroxide easily penetrates membranes and reacts slowly with superoxide. Hydrogen peroxide is a weak oxidizing agent and can react catalytically with transitional metals (iron and copper) to form the hydroxyl radical in what is known as the Fenton reaction.[35]

Hydroxyl radicals are the most reactive of the free radicals and react with almost any molecule (carbohydrates, lipids, proteins, or nucleic acid bases) within a few atomic collisions. Polyunsaturated fatty acids are particularly susceptible to hydroxyl radical attack, forming lipid radicals. This is the initial step in the chain reaction of lipid peroxidation.[114] Lipid radicals react with oxygen to form lipid hydroperoxides and other products (alkanes, alkenes, hydroxy and epoxy derivatives, ketones, and polyhydroperoxides). Most of these radical products are toxic to cells even in small quantities.

During ischemia, several events take place that predispose to the formation of free radicals (Fig. 6). Ischemia stops the production of ATP and the existing stores of ATP are rapidly metabolized for energy. As the cell's energy decreases, it is no longer able to maintain the normal ion gradients across the cell's membranes. This allows a massive influx of calcium. This metabolism of ATP also increases the cellular concentrations of AMP. AMP is metabolized to adenosine and inosine intermediates, and then to hypoxanthine. The elevated cytosolic calcium concentration can activate the protease calpain, which converts

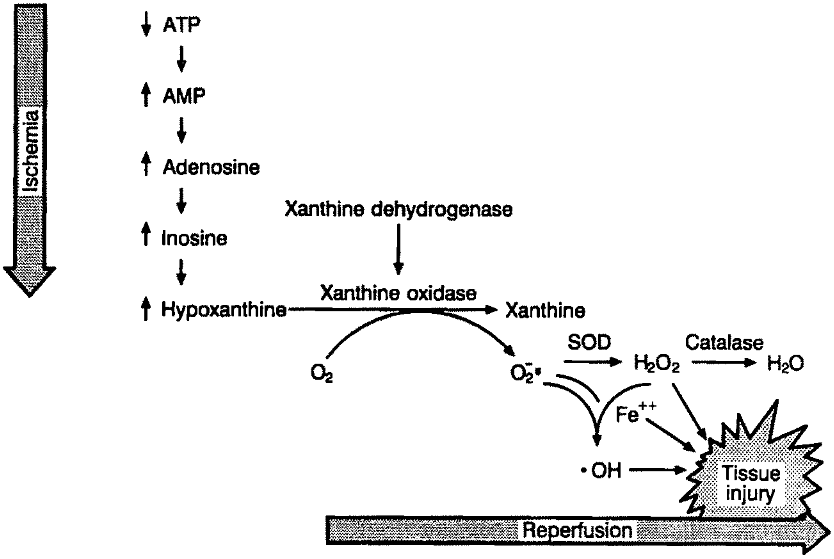

Figure 6. Mechanism of free radical generation in ischemic tissues following reperfusion and reoxygenation. With the onset of ischemia, ATP is metabolized to the adenine nucleotides and ultimately to the purine bases causing accumulation of hypoxanthine. During ischemia, xanthine dehydrogenase is converted to xanthine oxidase. During reperfusion and reoxygenation, hypoxanthine is converted to xanthine by xanthine oxidase, which produces superoxide radicals ($O_2^{-\bullet}$) as a byproduct. Using ferrous iron (Fe^{2+}) released during ischemia, superoxide radicals are converted to the more highly reactive hydroxyl radicals (•OH) in the Fenton reaction. Free radicals can destroy cellular membranes causing irreversible tissue damage.

xanthine dehydrogenase to xanthine oxidase. In addition, sulfhydryl oxidation in ischemic tissues can convert xanthine dehydrogenase to xanthine oxidase. Xanthine oxidase converts the hypoxanthine that has accumulated in the cells during ischemia to xanthine, reducing O_2 to the superoxide radical, $O_2^\bullet$, as a by-product. This appears to be the major source of superoxide radicals in postischemic tissues. During complete cerebral ischemia both free radical generation and the defense system against free radicals are limited. However, during reperfusion following ischemia, cells are again exposed to higher O_2 tensions. The formation of superoxide radicals is enhanced during the reperfusion following ischemia because of the abundance of reducing equivalents such as NADPH, which are produced in excess during ischemia, the action of xanthine oxidase, and the availability of molecular oxygen. This increased concentration of O_2 in the presence of inadequately functioning mitochondria, which were damaged during the ischemia, and decreased scavenging mechanisms may result in a high free radical load.[29] Intracellular levels of free iron may become increased during ischemia due to Ca^{2+}-mediated mitochondrial injury releasing the stores of mitochondrial iron and due to the release of free iron from ferritin.[115] This increased free iron concentration catalyzes the conversion of the superoxide radicals to the more highly reactive and toxic hydroxyl radicals.[19, 90] With reperfusion free radicals may also be generated as by-products of the oxidation of arachidonic acid (released from membrane phospholipids during ischemia) to produce prostaglandins and leukotrienes. Reduction of the hydroperoxide group of prostaglandin G_2 to form prostaglandin H_2 produces free radical intermediates that are reduced by nicotinamide adenine dinucleotide to generate more free radicals, all of which can donate an electron to O_2 to produce superoxide radicals.

It is believed that the cellular damage that occurs postischemia may be due in part to biochemical alterations produced by elevated levels of the superoxide and hydroxyl radicals.[115] Free radicals can react with and damage proteins, nucleic acids, lipids, and other classes of molecules.

Neuronal membranes are rich in polyunsaturated fatty acids and are especially susceptible to attack by free radicals at carbon-carbon double bonds. Peroxidation of the polyunsaturated fatty acids in lipid membranes severely damages cell membranes. Potential consequences of damage to membrane lipids include changes in fluidity and permeability and in the orientation of proteins embedded in the lipid bilayer of the cellular membranes. The shape and function of many intrinsic membrane proteins depend on specific interactions between their hydrophobic areas and the membrane phospholipids.[50] The more rigid membrane, which results from cross-linking of proteins within it by free radicals, causes changes in the activity of essential membrane proteins such as the sodium pump. This may lead to changes in the ion pumping rate of the membrane and disrupt transmembrane ion gradients.[16] The end products of lipid peroxidation are aldehydes, hydrocarbon gases, and other residue that can cause cytotoxic and vasogenic cell edema, alter vascular endothelial and BBB permeability, and produce inflammation and chemotaxis.[100] Superoxide radicals themselves can elicit an inflammatory response with a resultant influx of neutrophils that will respond by secreting oxygen radicals of their own and by forming vascular plugs thereby increasing cellular edema.[114]

The normal defense systems against free radical damage include spatial separation of radical generating reactions and target molecules, enzymatic systems that quench free radicals, and antioxidative enzymes that scavenge free radicals.[92] Free radical scavengers are molecules with a structure that imparts chemical stability to free radicals, thereby stopping the chain reaction of free radical generation. Free radical scavengers include superoxide dismutase directed against $O_2^{\bullet}$, catalase and glutathione peroxidase directed against H_2O_2, and vitamin E and ceruloplasmin directed against those radicals in lipid and aqueous phases. There are no enzymes that scavenge the hydroxyl radical but cell processes exist to prevent its formation.[92, 100] Superoxide dismutase catalyzes the conversion of two superoxide radicals to hydrogen peroxide and water. Catalase converts hydrogen peroxide into O_2 and H_2O while glutathione peroxidase uses hydrogen peroxide to oxidize glutathione. The brain contains only small concentrations of the free radical scavengers, superoxide dismutase, catalase, glutathione peroxidase, and vitamin E. Therefore, during reperfusion following ischemia, superoxide dismutase and catalase, capable of destroying the superoxide radicals formed during normal aerobic metabolism, are overwhelmed. This results in an increased concentration of superoxide radicals, some of which are converted to hydroxyl radicals by iron-catalyzed reactions.[7] Scavengers such as alpha-tocopherol (vitamin E) are lipid soluble and easily cross the BBB and enter cell membranes. Vitamin E neutralizes free radicals by donating hydrogen atoms, leaving an unpaired electron on the vitamin E molecule, but this free radical is harmless. Ascorbate (vitamin C) crosses the BBB less readily, but is actively transported into the brain by the choroid plexus. Vitamin C exists as a relatively unreactive free radical, which by combining with the superoxide or hydroxyl radicals prevents further propagation of chain reactions. Uric acid can scavenge hydroxyl radicals and can bind transitional metals to prevent hydroxyl radical formation. Transferrin can bind free iron, and plasma ceruloplasmin can convert ferrous to ferric iron. It is the ferrous state that catalyzes the Fenton reaction to form hydroxyl radicals.

Therapy designed to prevent postischemic damage by free radicals includes anoxic reperfusion to deliver free radical scavengers before reoxygenation; administration of specific free radical scavengers such as superoxide dismutase or catalase or the nonspecific scavenger, vitamin E, to scavenge free radicals and block the chain reaction formation of more free radicals; the binding of free iron by iron chelators such as deferoxamine to prevent the formation of hydroxyl radicals and the subsequent cell damage initiated by them; and inhibition of xanthine oxidase by allopurinol to block the formation of xanthine and the subsequent formation of superoxide radicals.

At present, free radical damage as a cause of neuronal cell injury or death is a possibility but not an established fact. While in vitro studies have reported that free radicals are capable of damaging CNS tissue, it is still unclear whether and where free radicals contribute to cerebral ischemic damage in vivo. It is difficult to directly observe superoxide and hydroxyl radicals in biologic systems because they are extremely short-lived and are produced only in minute quantities. The newer methods to assess free radical flux in vivo and quantification of oxidative damage to biomolecules provide data that demonstrate that these processes do play a role in cell death. The question of just what in vivo conditions are minimally sufficient to initiate processes leading to cell death is still unknown. It remains an unresolved question whether there is any significant parenchymal contribution to reperfusion-induced brain injury due either to free radicals or to reactions initiated by them. This must be demonstrated before it can be determined that early application of effective anti–free radical or antiperoxidative agents can promote survival and neurologic recovery after CNS injury. The efficacy of the administration of protective enzymes or free radical scavengers in ameliorating neurologic injury following cerebral ischemia is the subject of much investigation. The beneficial effect, if any, of such use of scavenging agents depends on the possibility of mediation of the pathology produced by free radicals, the biologic compatibility of the scavenging agents, the dosage used, and the ability to deliver the scavenger to act at the cellular site where the free radicals are causing injury.[101]

Steroids

It has been shown that certain glucocorticoid steroids in high concentrations can inhibit lipid peroxidation of cell membranes via intercalation into the cell membranes and can protect susceptible fatty acids within the membranes from peroxidative attack by oxygen free radicals.[46] A new class of steroids, the 21-aminosteroids, lack glucocorticoid activity.[62] The 21-aminosteroids readily cross the BBB and are extremely potent inhibitors of iron-catalyzed lipid peroxidation. If free radical destruction of membranes via lipid peroxidation contributes significantly to irreversible cell damage following ischemia, 21-aminosteroids may provide protection from these secondary consequences of ischemia.

It remains to be shown whether the 21-aminosteroids actually reduce free radical generation or lipid peroxidation in vivo. A few animal studies have investigated the efficacy of 21-aminosteroids in preventing neurologic injury following focal and complete global cerebral ischemia. U74006F and U74500A when given after ischemia have been demonstrated to protect some selectively vulnerable CA_1 hippocampal neurons and certain neocortical areas against ischemia and improve survival,[47] reduce ischemic brain edema,[123] and attenuate postischemic hypoperfusion.[48] U74500A can also bind iron, which may explain its greater efficacy against lipid peroxidation.

CONCLUSIONS

Resuscitation implies therapy given after the ischemic event. For cerebral resuscitation to be possible, ultimate neurologic damage must be due to both the ischemic period itself, during which no treatment is practical or possible, and to events that take place after the restoration of circulation and reoxygenation (Fig. 7). If these secondary consequences of ischemia do contribute significantly to the ultimate neurologic damage, then therapy aimed at preventing these processes should affect outcome. These secondary consequences of ischemia have been described and evidence has been presented that these processes do indeed contribute to the ultimate neurologic damage. However, there is still little convincing evidence that therapy designed to prevent individual processes is efficacious in preventing neurologic damage. When the cellular mechanisms are better understood, it may be rational to combine therapy aimed at all the secondary processes. Cerebral resuscitation is possible, but it is not yet a reality.

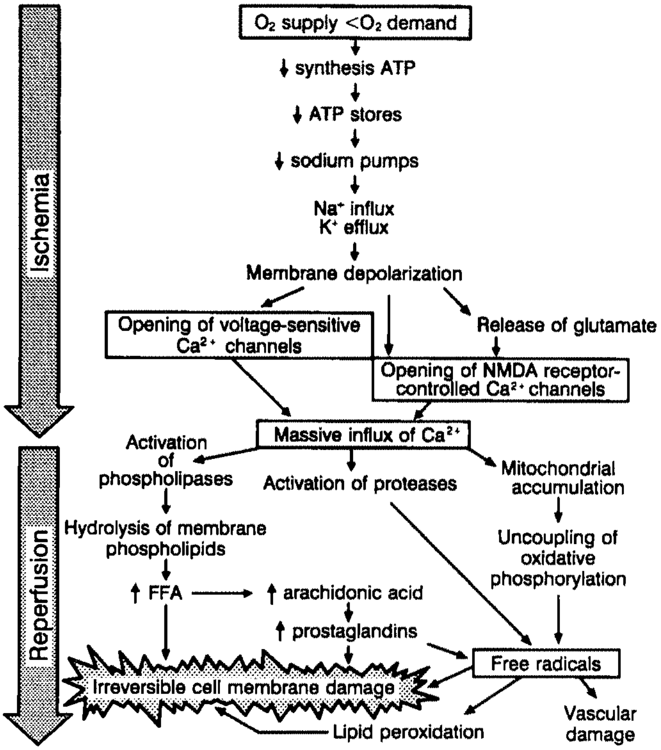
Ischemia
Reperfusion
O_2 supply <O_2 demand
↓ synthesis ATP
↓ ATP stores
↓ sodium pumps
Na^+ influx
K^+ efflux
Membrane depolarization
Opening of voltage-sensitive Ca^{2+} channels
Release of glutamate
Opening of NMDA receptor-controlled Ca^{2+} channels
Massive influx of Ca^{2+}
Activation of phospholipases
Activation of proteases
Mitochondrial accumulation
Hydrolysis of membrane phospholipids
Uncoupling of oxidative phosphorylation
↑ FFA
↑ arachidonic acid
↑ prostaglandins
Free radicals
Irreversible cell membrane damage
Lipid peroxidation
Vascular damage

Figure 7. The relationship between ischemic and reperfusion cellular changes leading to irreversible cell death.

SUMMARY

Recent research has indicated that intracellular events occurring during ischemia or after the restoration of circulation and oxygenation following an ischemic event contribute to the ultimate neurologic damage. There are several secondary consequences of ischemia that may produce neuronal damage resulting in neurologic dysfunction following ischemia. Ischemia produces depolarization of neurons, which allows influx of Na^+ and Ca^{2+} into the cells. Ischemia and depolarization also cause the release of glutamate, which activates NMDA receptors that control the influx of Na^+ and Ca^{2+}. When the ATP energy sources within the neurons are depleted, the energy-requiring ion pumps within the cell membrane cannot pump out Na^+ or Ca^{2+}. This results in intracellular Ca^{2+} overload and mitochondrial sequestration of Ca^{2+}. Increased intracellular Ca^{2+} initiates a cascade of events including the formation of prostaglandins, the formation of free radicals, and, ultimately, the destruction of cell membranes and mitochondria, causing irreversible cell damage. During ischemia, the substrate for the formation of free radicals accumulates so that during the recirculation period with reoxygenation, there is an increased production of free radicals that overwhelm the normal free radical scavenging systems. These free radicals are capable of producing widespread cellular damage, including peroxidation of polyunsaturated lipids and the cross-linking of proteins within the cell and mitochondrial membranes, which alter the shape and function of the membranes causing irreversible cell injury.

Therapy has been designed to block these secondary processes of ischemia. Calcium entry blockers can prevent the entry of calcium into cells. There is some evidence that these agents, even when given after the ischemic event, do provide some protection against the ultimate neurologic damage. Antagonists to the NMDA receptor–ion channel complex have been developed that either competitively block the NMDA receptor itself, noncompetitively block the ion channel, or competitively block the glycine receptor on the complex. A new class of glucocorticosteroids, the 21-aminosteroids, has been demonstrated to prevent lipid peroxidation. These agents have not been completely studied. Some studies do suggest that treatment with these agents after the ischemic event can ameliorate the ultimate neurologic damage. Free radical scavengers have also been developed that may have some efficacy against the damage produced by free radicals following ischemia. Further study must be done into the biochemical and pathophysiologic mechanisms that occur during and following ischemia. When these mechanisms are better detailed and understood, therapy can be rationally designed to prevent these processes.

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ANESTHETIC MANAGEMENT OF PATIENTS WITH HEAD INJURY

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Head injury is a major public health problem, with approximately 500,000 new cases occurring annually in the United States, of which 70% are mild, 10% to 20% are moderate, and 5% to 10% are fatal.[29] The frequency of fatal head injury is approximately 25 per 100,000 population in developed countries and 50% to 60% of these fatalities occur in the prehospital period, within moments of the injury.[29] Changes in this death rate will only occur with behavioral and engineering changes, and interventional medicine probably has little to offer. However, a proportion of these currently fatal injuries, as well as the mild-to-severe cases, represent a large reservoir of morbidity and mortality for which vigorous care may affect outcome. Emergency care is directed toward the diagnosis and surgical evacuation of significant intracranial hematomas and the treatment of factors that may result in a secondary insult to the brain. The latter may include airway obstruction, intracranial hypertension, circulatory shock, hypoxemia, hypercarbia, fluid and electrolyte disturbances, and obstructive hydrocephalus.

CLASSIFICATION

The Glasgow Coma Scale[53] (GCS) (Table 1) is a classification system that enables the physician to standardize the clinical description of the neurologic condition of the head-injured patient. This system facilitates comparison of groups of patients treated in different centers or with different treatment protocols. As can be seen from Table 1, the GCS is based on neurologic function, not on the pathologic characteristics of the injury. Head injuries with

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Table 1. THE GLASGOW COMA SCALE[53]

Eye opening		**Best verbal response**	
Spontaneous	4	Oriented	5
To speech	3	Confused	4
To pain	2	Inappropriate words	3
No response	1	Incomprehensible sounds	2
		No response	1
Motor response			
Obeys commands	6		
Localizes	5		
Withdraws	4		
Flexes	3		
Extends	2		
No response	1		

From Teasdale G, Jennett B: Assessment of coma and consciousness; a practical scale. Lancet 2:81, 1974; with permission.

a GCS of 8 or less are usually classified as severe. The motor component of the GCS correlates inversely with mortality.[8]

PATHOPHYSIOLOGY

Head injury encompasses many different forms of trauma to the skull and brain and therefore discussion of the pathophysiologic events following head injury are subdivided into intracranial hematomas (epidural, acute subdural, and brain contusion), brain edema, and systemic effects of head injury.

Intracranial Hematomas

Epidural

Most frequently caused by arterial bleeding from a middle meningeal artery torn in the course of a fracture of the temporal bone, an epidural hematoma is one of the true neurosurgical emergencies. This injury is present in approximately 2% of patients with head injuries.[8] The rapid expansion of the hematoma, driven by systemic arterial pressure, can quickly result in herniation of the temporal lobe, which may be accompanied by ipsilateral pupillary dilation as a sign of compression of the third nerve against the tentorium by the temporal lobe. Temporal lobe herniation (see following) is one of the syndromes of rostrocaudal deterioration summarized by Plum and Posner.[37] Recently, the relationship between the degree of brain shift and the level of consciousness has been confirmed, although the role of uncal herniation in the syndrome has been questioned.[42, 44]

Acute Subdural Hematoma and Brain Contusion

Subdural blood seen on computed tomography in the acute period following head injury usually has its source in a hemorrhagic cortical contusion. The mass effect of the contused and edematous brain may prompt surgical removal if the brain region involved is not functionally important.

Recent investigations using positron emission tomography have studied cerebral hemodynamics in patients with brain contusion.[23, 54] In the contused brain, cerebral metabolism and blood flow were reduced 50%. A similar pattern of hemodynamic changes was observed in brain regions remote from the contusion. It is not known whether these widespread changes in cerebral metabolism observed in head-injured patients reflect mechanical effects of the injury (increased intracranial pressure [ICP], cerebral edema) or functional cerebral depression.[34]

NEUROLOGIC ASSESSMENT OF THE HEAD-INJURED PATIENT

The goal of this assessment is to identify those patients who have an intracranial hematoma or mass lesion that may cause brain shift and precipitate herniation. Clinical signs concerning the level of consciousness, respiratory pattern, pupillary size and reactivity, and motor response to stimulation are important indicators that brain herniation is imminent. Two syndromes have been described: the *central syndrome* of rostral-caudal deterioration and the *syndrome of uncal herniation.*[37]

Central Rostral-Caudal Deterioration

Patients with a centrally placed expanding lesion, which focuses pressure on the diencephalon and upper midbrain (Fig. 1), commonly present the

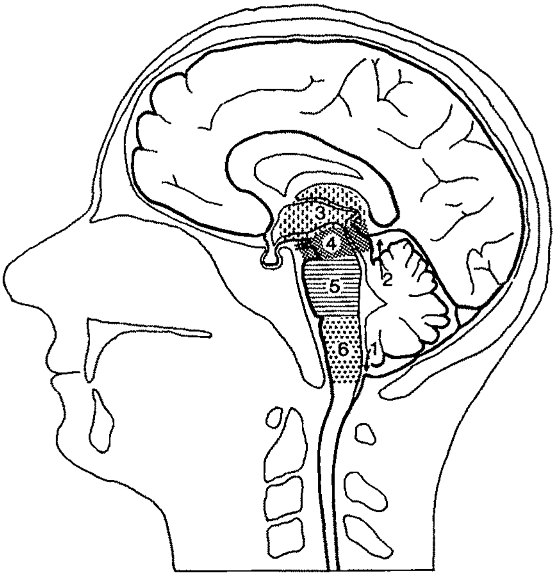

Figure 1. Schematic diagram demonstrating the principal structures that may be involved in brain herniation. In the syndrome of central rostocaudal deterioration, pressure is focused on the diencephalon (3) and upper midbrain (4), causing alteration in the level of consciousness. The cerebellum may herniate either down through the foramen magnum (1) or up under the tentorium (2). Cerebellar = 1; cerebellar vermis = 2; pons = 5; medulla = 6. (*From* Archer DP: Intracranial pressure: Anesthetic considerations. Progress in Anesthesiology 2:2–12, 1987; with permission.)

following neurologic picture.[3] Early signs of diencephalic dysfunction may be subtle: a loss of interest in surroundings, agitated or garrulous behavior, and fluctuation in the level of consciousness. Progressive somnolence follows. The respiratory pattern may be normal or frequent yawns and sighs may be present. Occasionally there may be Cheyne-Stokes respiration. In the early stages, the patient withdraws normally from painful stimulation.

As the pressure cone progresses caudally, upper midbrain dysfunction is associated with midsize irregular pupils and bilateral flexion motor responses. Cheyne-Stokes respirations or sustained hyperventilation are characteristic of this stage. It is important to intervene in the early diencephalic or upper midbrain stage because beyond these levels progressive distortion of the brain stem structures may rupture the blood vessels from the basilar artery that penetrate the brain stem.

Uncal Herniation

Laterally placed masses may shift the medial aspect of the temporal lobe (uncus) across the tentorial edge and onto the midbrain. In this process the cranial nerve III is compressed (Fig. 2). Consequently, pupillary dilatation ipsilateral to the lesion is an early sign of brain shift in this form of herniation. In contrast to the central syndrome, consciousness may be preserved. Intervention at this stage is important to prevent cardiorespiratory collapse from medullary compression.

With these two syndromes in mind, the anesthesiologist should assess whether the head-injured patient has a brain injury or intracranial hematoma. The level of consciousness should be documented with the GCS and evidence of posttraumatic amnesia sought.

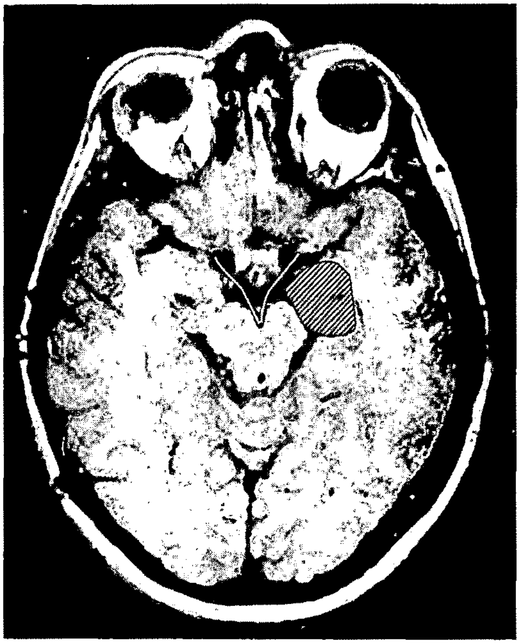

Figure 2. Axial magnetic resonance scan at the level of the upper midbrain (area 4 in Fig. 1), demonstrating the relationship between the uncus of the temporal lobe (*hatched*) and the third cranial nerve (*white line*). An early sign of temporal lobe herniation is dilation of the ipsilateral pupil due to pressure on the third nerve. (*From* Archer DP: Intracranial pressure: Anesthetic considerations. Progress in Anesthesiology 2:2–12, 1987; with permission.)

Any patient who has evidence of brain injury should have a neurosurgical evaluation and, if feasible, a computed tomographic scan to rule out intracranial hematoma before general anesthesia. In the presence of diffuse swelling or a small hematoma to be evacuated later (e.g., after splenectomy), ICP monitoring may be indicated when clinical evaluation is not possible (e.g., during anesthesia).

Intracranial Pressure

In patients with syndromes of herniation, control of the ICP is likely to be very important. Because of the clinical setting in which these patients are treated, it is very uncommon to have ICP measurements to correlate with clinical and pathologic findings. Consequently, much of our information is extrapolated from data generated in the laboratory.

In normal individuals in the supine position, the pressure within the cerebral ventricles and in the lumbar subarachnoid space may be as high as 10 mm Hg. This static cerebrospinal fluid pressure (CSFP) is that which is sufficient to cause CSF reabsorption to equal production. As shown in Figure 3, CSF reabsorption increases with increasing CSF pressure, while production is affected little until CSFP reaches very high values. The equilibrium CSFP occurs when the CSF production curve intercepts the CSF reabsorption curve (Fig. 3). Increased resistance to CSF reabsorption results in a flattening of the reabsorption curve, moving the intercept from P1eq to the higher value at P2eq.

The expansion of an intracranial mass alters the static relationship and increases the CSFP. The traditional description of these events is that initial compensation for the expanding mass is accomplished by dislocation of CSF and blood volume. During this phase, the CSFP increases only slightly. As the capacity for volume compensation is exhausted and intracranial elastance (change in CSF volume with change in CSFP) decreases, CSFP increases progressively. The decrease in elastance may be quantified clinically by measuring the increase in CSFP that occurs on injection of 1 mL of fluid into the subarachnoid space and calculating the volume to pressure ratio.[27] Brain shift correlates with the volume to pressure ratio rather than with the CSFP.[27]

In contrast with the conventional view, expansion of an intracranial balloon caused cerebral blood volume to increase, not decrease, probably due to vasodilation.[18] Recent investigations have suggested a different explanation for

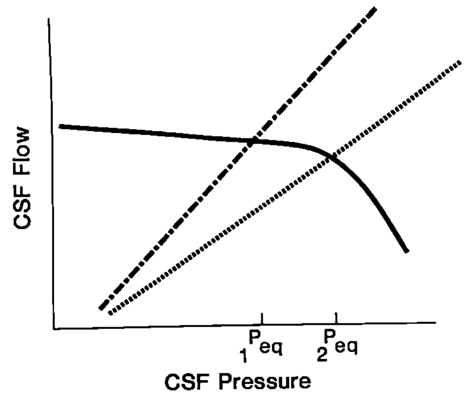

Figure 3. Equilibrium CSF pressure P1eq is that pressure at which the CSF production (——) equals the CSF reabsorption (-•-). With increased resistance to CSF outflow (---) caused by distortion of CSF pathways after trauma, these curves intercept at a higher value for CSF pressure, P2eq. (*Adapted from* Sullivan HG, Miller JD, Searle JR: An interpretation of pressure/volume interactions in the craniospinal axis. Neurosurgery 6:453–462, 1980; with permission.)

the shape of the pressure/volume curve outlined previously. Sullivan and colleagues[51] have suggested that the flat portion of the intracranial compliance curve represents the condition in which the pathways for CSF drainage are open, with normal resistance to CSF outflow. Subsequent increases in supratentorial pressure occur as the resistance to CSF outflow increases, likely due to anatomic distortion of CSF pathways by the expanding mass lesion or consequent brain shift. They suggest that a significant gradient between the supratentorial and infratentorial compartments exists at supratentorial ICP values of 20 mm Hg or greater and that the gradient increases as the supratentorial ICP increases.[52]

How large must an increase in ICP be in order to be of biologic significance? The clinical situation of the herniating patient has been most closely approximated in the laboratory by animal models in which an epidural balloon is inflated in the supratentorial epidural space. As the intracranial mass enlarges, the gradient between supratentorial and infratentorial pressures increases.[52] Fitch and McDowall[15] demonstrated that introduction of halothane increased the transtentorial pressure gradient and the supratentorial pressure. Pupillary size was observed as an indicator of transtentorial herniation. Pupillary dilation was noted after modest and sometimes small changes in supratentorial pressure (Fig. 4).

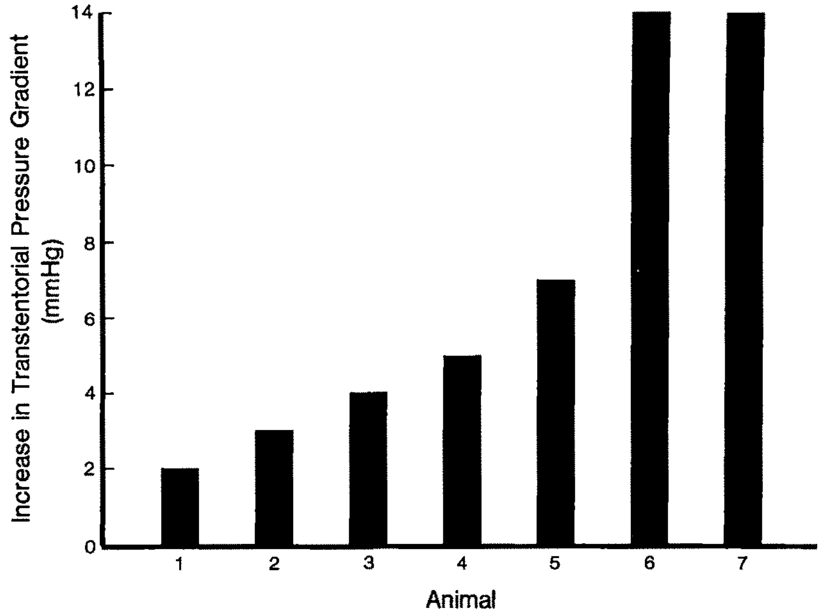

Figure 4. The increases in transtentorial CSF pressure gradient associated with pupillary dilatation in the dog. Baseline ICP was increased by inflating an intracranial epidural balloon. The additional increase in CSF pressure difference between the lateral ventricle and the cisterna magna caused by the introduction of halothane was associated with a sign of temporal lobe herniation. Note that the increases in the pressure gradient in animals 1 to 5 were quite small. (*Data from* Fitch W, McDowell DG: Effects of halothane on intracranial pressure gradients in the presence of intracranial space occupying lesions. Br J Anaesth 43:904–911, 1971.)

Traumatic Edema in Head Injury

Brain edema following head injury is a complex combination of vasogenic and cytotoxic edema.[55] Unlike the experimental models that have been used in the laboratory to describe factors important in edema formation and resolution,[35] brain edema following head injury is a highly variable secondary response to injury. Injury sufficient to produce tissue hemorrhage results in extravasation of protein-rich fluid *(vasogenic edema)* through the disrupted blood–brain barrier. The edema moves into white matter under hydrostatic pressure, and a major portion of this fluid is absorbed into the cerebral ventricles. In the experimental setting, the extent and amount of edema depends primarily on the surface area of the vasculature that has been damaged and on the pressure gradient between the intravascular pressure and the perivascular tissue pressure.[55]

White matter edema occurring in the absence of tissue hemorrhage is protein poor, and the mechanism for formation of this edema fluid in head injury is unknown.[55]

Cellular edema occurs after head injury, independent of extracellular edema, and may be in response to metabolic perturbations following injury such as the absorption of extracellular fluid and electrolytes by glia.[55]

Despite major research efforts in the last three decades, specific therapy for brain edema in head injury is lacking. Mannitol and other hypertonic solutions used to reduce brain bulk and ICP probably remove water only from tissue with an intact blood–brain barrier.[36] Steroids, while effective in reducing vasogenic edema surrounding brain abscesses and tumors, have been shown not to be beneficial in head injury.[13] Pentobarbital has been shown not to be associated with decreased edema formation in vasogenic edema.[20]

Cerebral Blood Flow Following Head Injury

Patients with head injury show wide variation in cerebral blood flow, and isolated cerebral blood flow measurements correlate poorly with outcome, although both very high and very low flows tend to have a poor outcome.[33] If hyperemic patients are excluded, then a relationship between cerebral blood flow and outcome can be demonstrated, with higher blood flows being associated with better outcome.[19] These results are consistent with the interpretation[45, 31] that patients with reduced cerebral metabolism ($CMRO_2$ less than one third of the normal value) have a poorer prognosis than those with higher values and that the low cerebral blood flow is simply a marker for the reduced metabolic rate. (Cerebral blood flow values < 35 mL/100 g/min have been shown to be coupled to $CMRO_2$.[32]) Recent experimental evidence also suggests that oxygen metabolism may be impaired by ICP values over 18 cm H_2O.[4]

Cardiovascular and Metabolic Response to Head Injury

Head injury evokes a hypermetabolic response in the rest of the body that is most severe in the pyrexic patient with spontaneous decerebrate posturing. This hypermetabolic state is similar to that present in a patient with a 20% to 40% burn. Oxygen consumption and cardiac index are increased by 14% and 30%, respectively. Because systemic vascular resistance changes little, mean arterial pressure increases approximately 18%. The severity of the head injury is a factor in the metabolic expenditure; patients with posturing responses (GCS 4–5) have a significantly higher metabolic expenditure than those who are localizing (GCS 6–7). Overall, head-injured patients have an average daily resting metabolic expenditure of 2500 kcal. (An average sedentary adult expends 1500 kcal/d.)

Cardiovascular evaluations of multiply injured patients have emphasized that following resuscitation from shock or injury there is normally a hyperdynamic response. Failure to achieve this state is seen in some patients with a low output state characterized by low cardiac filling pressures, low cardiac index and oxygen consumption, and low arterial pressures. Although it is not clear that manipulation of the cardiovascular system to increase oxygen delivery results in improved outcome, desirable guidelines for hemodynamic management have nonetheless been proposed by Shoemaker and colleagues.[48] In contrast to the traditional teaching of "keeping the patient dry" in the hope of preventing or reducing cerebral edema,[47] some authors are now advocating the maintenance of normovolemia and support of the cardiovascular system if necessary to optimize cardiac index and oxygen delivery.[43] In the experimental setting,[4] intracranial pressures above 18 cm H_2O have been found to increase the brain pyridine nucleotide oxidation/reduction (redox) balance ([NADH]/[NAD^+]), suggesting that cellular oxygen metabolism was impaired. Increasing inspired oxygen concentration from 0.21 to 0.5 blunted the increase in redox balance in the ICP range of 18 to 36 cm H_2O. FiO_2 values greater than 0.5 conferred no further benefit.

Pulmonary Response to Head Injury

Frequent causes of hypoxemia in head-injured patients include pulmonary aspiration of pharyngeal or stomach contents, chest trauma, fat embolism, seizures, and neurogenic pulmonary dysfunction.[6] The pulmonary response to head or high cervical spine injury in humans is not well understood. From studies of experimental head injury, reviewed by Beckman,[6] it appears that there are major differences between species and between injury models in the effects of head injury or intracranial hypertension on the lung. In some studies vascular pressures increase abruptly after head injury, leading to both high pressure and low pressure (by increased capillary permeability) pulmonary edema. In other reports protein-rich lung lymph and pulmonary edema fluid are formed after head injury without any changes in vascular pressure. In the latter studies it is not even clear that capillary permeability is increased, for some authors believe that the changes can be accounted for by capillary recruitment.

Treatment for neurogenic pulmonary dysfunction is primarily that of the underlying intracranial disorder, evacuation of hematoma or reduction of intracranial hypertension. The effectiveness of diuretics in this situation is difficult to assess because the condition is usually transient and the diuretics act to reduce both pulmonary vascular and intracranial pressures. Intraoperatively, with the patient head-up 15 to 30 degrees, application of 5 to 10 cm of positive end-expiratory pressure during controlled hyperventilation with an increased FiO_2 is usually effective in reversing the hypoxemia without increasing ICP.[2, 9]

Coagulopathy in Head Injury

Brain tissue injury can activate the coagulation cascade through endothelial injury (intrinsic pathway) and through the release of tissue thromboplastin into the circulation (extrinsic pathway).[56] Coagulation studies (plasma fibrinogen and fibrin degradation product concentrations) are abnormal in 40% of patients with closed head injury, while 8% of patients have evidence of disseminated intravascular coagulation.[22] Surgical debridement of damaged brain may limit the primary process, and because of the risk of bleeding, replacement of depleted factors should be considered early in the course of the coagulopathy. The use of heparin and epsilon amino caproic acid to limit clotting and prevent clot lysis, respectively, has been suggested, but we are aware of no evidence supporting their use in head-injured patients.

ANESTHETIC MANAGEMENT

Resuscitation and stabilization of the patient with head injury proceed in the same fashion as for any trauma victim. Initially emphasis is on assessment and support, if necessary, of the airway, ventilation, and circulation. The use of pulse oximetry, capnography, and oscillometric automated blood pressure determination greatly facilitate the initial assessment of the patient. In the patient with an isolated head injury, care must be taken during the secondary survey to rule out major thoracoabdominal injuries before proceeding to craniotomy. Neurologic examination is focused on the detection of intracranial hematomas and particularly on the herniation syndromes outlined previously. Close attention to cardiorespiratory management during computed tomographic scanning permits the detection of occult injuries and prevents deterioration during a period when the patient is often not closely observed.

Airway Management and Mechanical Ventilation

Endotracheal intubation and mechanical ventilation are frequently indicated in head-injured patients either as supportive management of the unconscious patient or as treatment for intracranial hypertension. Control of the airway by tracheal intubation is often urgently required because of coexisting trauma to the respiratory system, cardiovascular compromise, or to prevent brain herniation. The possibility of a cervical spine injury in these patients imposes the additional constraint that spinal movement must be avoided. The prediction of cervical spine injuries by clinical characteristics is inexact and fractures are sometimes not detected on suitable plain films of the neck.[11] It is therefore wise to be cautious in manipulating the neck of patients whose neck "has been cleared," because the major factor in the more than sevenfold increase in secondary neurologic injury in patients with undiscovered cervical spine injury is failure to immobilize the neck.[11] Neck stabilization would appear to be best accomplished with the head restrained between sand bags with 3-inch cloth tape combined with a Philadelphia collar.[11] Manual in-line traction, although it may cause distraction of upper (C_1–C_2) cervical spine fractures, has a good safety record[17] and is very helpful during intubation of patients with acute respiratory compromise.

Many different methods of intubation including blind nasotracheal, fiberoptic orotracheal and nasotracheal, retrograde catheter guided,[1] and orotracheal laryngoscopic have been advocated. In a recent review of this issue, Crosby and Lui[11] could not find evidence in the literature that any particular mode of intubation was superior. They recommend that physicians responsible for securing the airway in patients with potentially injured cervical spines develop an algorithm for management using the method(s) with which they have the most expertise.[11]

The stimulation of the sympathetic nervous system that occurs during laryngoscopy and intubation raises ICP, sometimes considerably (Fig. 5).[30] The significance of increases in ICP has been the subject of controversy.[12, 26] Considering the current concepts regarding herniation and ICP outlined previously, control of ICP would appear to be important, particularly in patients with herniation syndromes.

The upper airway should be cleared and any obstruction eliminated if possible. Assisted ventilation with oxygen may significantly improve blood gas tensions and intracranial compliance. If mannitol administration is planned and there is time, start the infusion before intubation in order to further reduce ICP before intubation. Although control of ICP can be achieved using mannitol in repeated doses of 0.25 g/kg,[24] a larger dose of 1 g/kg has been reported to be effective in herniating patients.[59] If appropriate, good intubating conditions should be provided with an induction sequence of an intravenous barbiturate, propofol or etomidate, lidocaine, 1.5 mg/kg 90 seconds before intubation, and a muscle relaxant.[5] If rapid control of the airway requires the use of succinylcholine, a defasciculating dose of metocurine (0.03 mg/kg) given 3 minutes before induction will blunt the increase in ICP that sometimes occurs with succinylcholine.[50]

The effectiveness of hyperventilation in the head-injured patient is somewhat controversial. Hyperventilation to produce hypocapnia is one of the maneuvers used to reverse herniation.[58] Ward et al[57] reported that prophylactic hyperventilation did not improve outcome in severely head-injured patients. The authors' view is that hyperventilation is one of methods of reducing ICP in patients at risk from herniation and should be used acutely to stabilize the patient. The role of long-term hyperventilation is less certain, but normocapnia should be restored with caution because cerebral blood flow and ICP can be expected to increase acutely as $Paco_2$ increases.

Many patients spontaneously hyperventilate; for them, insertion of a tracheal tube may be indicated to protect the airway against aspiration of pharyngeal and stomach contents. In general, we secure the airway if the GCS

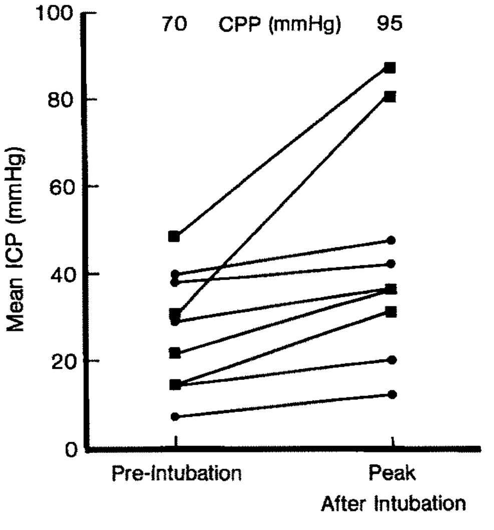

Figure 5. ICP before and after tracheal intubation using a barbiturate, succinylcholine induction sequence. Note that although cerebral perfusion pressure was well maintained, some patients had large increases in ICP. (*Adapted from* Misfeldt BB, Jorgensen PB, Risoj M: The effect of nitrous oxide and halothane upon the intracranial pressure in hypocapnic patients with intracranial disorders. Br J Anaesth 46:853–858, 1974; with permission.)

is 8 or less. This usually means that the patient does not respond vigorously and purposefully to a painful stimulus. Other indications for tracheal intubation include uncontrolled convulsions, ICP > 25 mm Hg despite diuretics or CSF drainage, and a combination of head and chest injuries.

Maintenance of Anesthesia

In many cases induction of anesthesia and institution of controlled hyperventilation greatly reduce ICP, and any effects of drugs such as succinylcholine, isoflurane, halothane, sufentanil,[25] and nitrous oxide to increase ICP are obscured by the increase in intracranial compliance postinduction. Thus, the use of a combination of nitrous oxide, isoflurane, and opiates was very satisfactory for the maintenance of anesthesia in a recent study of patients undergoing craniotomy for supratentorial tumor (some of whom probably had raised ICPs), and no important differences were found among the patients treated with alfentanil, fentanyl, and sufentanil.[16]

The problem patients are those in whom the measures to decrease ICP described previously have not been sufficient to reverse signs of herniation. These patients may still deteriorate rapidly and irreversibly if the ICP is acutely raised. Two studies have shown that when halothane or isoflurane were administered to animals with intracranial mass lesions, ICP increased significantly, despite prior hyperventilation.[46, 49] For this reason we avoid volatile agents before dural opening in patients with herniation syndromes. A thiopental infusion (14 mg/kg/hr) is a convenient way to deepen anesthesia and reduce ICP during the period before dural opening.[10]

Brain swelling occurring during maintenance of anesthesia should prompt a review of the adequacy of hyperventilation (Pa_{CO_2} 25–30 mm Hg) and oxygenation, anesthetic depth, and degree of neuromuscular blockade. Endobronchial intubation and unsuspected pneumothorax must be ruled out. Head and neck position should be assessed and adjusted if necessary to ensure adequate cerebral venous drainage with 30 degrees elevation of the head without kinking of the neck veins. The possibility of pneumocephalus must be considered if nitrous oxide is used.

Fluid Management

The maintenance of normovolemia in the head-injured patient is frequently complex, and consideration should be given to guiding fluid management with specific cardiovascular end points, as outlined previously, rather than by a formula based on body weight. Fluid management for the neurosurgical patient has been reviewed recently.[14] The factor in the administered fluid that most affects brain water content is the osmolality,[60] making iso-osmolar solutions the best choice for intravascular volume replacement. Lactated Ringer's solution (250–260 mOsm/kg) is hypo-osmolar to plasma (285–290 mOsm/kg) and, therefore, administration of large volumes of Ringer's should be avoided. Lowering colloid osmotic pressure does not increase brain water in normal or injured brain.[21] Rapid administration of 10 mL/kg of normal saline had little effect on cerebral blood volume or ICP in normal dogs.[39] Rapid administration of mannitol increases cerebral blood volume and central venous pressure and decreases blood pressure.[40] These acute hemodynamic changes are accompanied by an increase in ICP in individuals with normal initial ICP but not in patients with increased ICP.[41]

The urine output may be increased in volume due to the hyperdynamic state outlined previously or due to mannitol or furosemide administration. The urine may be altered in composition by either of these diuretics or by hormonal imbalance such as diabetes insipidus or the syndrome of inappropriate antidiuretic hormone secretion.

Diabetes insipidus is confirmed when urine osmolality is less than 300 mOsm/kg when plasma osmolality is greater than 295 mOsm/kg. Treatment is with vasopressin tannate in oil intramuscularly, or with desmopressin acetate, intranasally.

The syndrome of inappropriate antidiuretic hormone secretion is a diagnosis of exclusion based on the finding of hyponatremia in the absence of hypovolemia or sodium retention (no evidence of edema, congestive heart failure, and normal blood urea nitrogen, creatinine, and sodium concentrations in the urine (> 40 mEq/L). Treatment is usually by water restriction to 500 mL/d.

Hyperglycemia occurs frequently in head-injured patients and is thought to be a good indicator of the severity of the injury and a predictor of outcome.[58] Whether hyperglycemia in this setting is a factor in the outcome or whether it is simply a marker for the severely injured has not to our knowledge been established.

SUMMARY

Among head injury victims are patients who have signs of brain shift and raised ICP. The goals of anesthetic management for these patients include the initial resuscitation and stabilization of cardiorespiratory function and the reduction of ICP. Two neurologic syndromes, central rostrocaudal deterioration and uncal herniation, identify individuals with critically increased ICP. Adequate oxygenation, ventilation, and mannitol administration will help to reduce ICP before intubation of the trachea. Stabilization of the cervical spine to prevent movement is vital during intubation for patients in whom the status of the spine is uncertain. Although cerebral perfusion pressure is well preserved during hypertensive episodes following tracheal intubation, the accompanying increase in ICP may precipitate herniation in those with herniation syndromes. Consequently, methods to blunt the hypertensive response to intubation may be life-saving in patients with reversible intracranial pathology. Fluid administration in these patients should be guided by the usual requirements for trauma victims, avoiding lactated Ringer's solution in favor of iso-osmolar solutions such as normal saline. The colloid osmotic pressure does not appear to be important in the formation of brain water in either normal or injured brain. Hyperglycemia, although associated with worse outcomes in head injury patients, may be either a factor or a marker for brain injury.

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CARDIOPULMONARY RESUSCITATION AND CEREBRAL OUTCOME

Is There Any Hope?

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If the history of cardiopulmonary resuscitation (CPR) and reanimatology bears any reflection on the future, one can only speculate on what lies ahead. Closed chest CPR was originally reported by Kowenhoven and colleagues over 30 years ago. The current clinical, electrical, and pharmacologic bases of CPR have become firmly established as a standard by which any alterations in technique are compared. It would seem that the current techniques of CPR have produced what is today regarded as the maximal limits of resuscibility. Intensive research is now required to extend our knowledge about the limits of injury reversibility and ways in which we can apply this knowledge to benefit cerebral outcome. A gradual if not a dramatic extension of these limits will make quality survival from cardiopulmonary arrest far more common than it is today.

HISTORY

The history of resuscitation closely parallels the evolution of modern medicine. Excellent monographs reflecting this development can be found elsewhere.[7, 127] The following short history tries to capture significant moments in the recent history of CPR.

Reanimatology is the science of resuscitation. Modern cardiopulmonary cerebral resuscitation spans a mere three decades. This has been aptly termed

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"the resuscitation age." When one considers that the history of CPR extends from biblical times, the modern evolution of cardiopulmonary cerebral resusitation has been explosive. Beginning as a number of isolated techniques, each described individually by the turn of this century, the present synthesis of chest compressions, exhaled air ventilation, and electrical defibrillation required the insight of thoughtful professionals, such as Elam, Gordon and Safar (anaesthetists), Jude (a surgeon), and Knickerbocker and Kouwenhoven (electrical engineers) to combine and formulate the present life support system.

The culmination occurred in 1959, with the presentation of the combined basic life support system by Safar to the Maryland Medical Society, and persists today with few significant refinements. Advanced life support was added shortly after. The American Heart Association CPR Committee, initiated in 1963, published the national standards of basic CPR plus definitive therapy in 1966.[3] This rapidly disseminated throughout the world and remains the accepted standard today.

During the late 1960s and 1970s, CPR public education schemes proliferated throughout North America and spread to Europe and Australia. Practical training had been augmented by the development of the Resusci-Anne manikin by Asmund Laerdal in Norway. First introduced in 1960, it has become a sophisticated multipurpose teaching aid.

Self-inflating bags and nonrebreathing valves were invented by Ruben in the late 1950s. There are many varieties available today based on a similar principle. These pieces of equipment have become essential for the resuscitation cart.

It was realized early in the evolution of modern reanimatology that basic life support had to be taken to the community if the full benefit of CPR was to realized. Once the importance of ventricular fibrillation was appreciated, it was also quickly understood that advanced life support had to become mobile and transportable. The first mobile coronary care ambulance service was established in Belfast by Pantridge in 1967. His example was rapidly emulated across the United States in the late 1960s and 1970s, but much less enthusiastically in Europe. Pantridge is also credited with the first miniature portable defibrillator.

The development of relatively safe anaesthetics allowed surgery to become not only more humane, but served as a platform for the development of specialty surgical refinements. The operating theatre allowed the anesthetist to assume a central role in modern airway control. The sudden unexpected deaths while administering ether or chloroform anesthetics in the mid-nineteenth century were an impetus for resuscitation of the arrested heart. This was initially by open cardiac massage, followed by the discovery of the efficacy of closed chest cardiac massage.

As surgery became more sophisticated, greater demands were placed on the anesthetist. An obvious need for more intensive monitoring developed, both during and after surgery, to provide the level of surveillance necessary for patient safety. The postoperative recovery room, initially conceived by a neurosurgeon, Walter Dandy, was extended into postsurgical intensive care units (ICUs) by anesthetists in some centers in the United States by 1950.

Respiratory intensive care was pioneered by the Scandinavians in the early 1950s when the great polio epidemics created widespread respiratory insufficiency. Prolonged manual intermittent positive airway pressure preceded mechanical machinery. The early landmark developments in ICU were associated with mechanical ventilation. Subsequent developments have chronologically moved through elucidating the etiology and correction of the different shock states, the etiology and support of multiorgan dysfunction, nutritional and metabolic support, and more recently to organ transplantation. Adult ICUs provided the impetus for the development of intensive monitoring and support of the critically ill pediatric patient. The first pediatric ICU was established by the late 1960s in Philadelphia. The first coronary care unit was established in the United States in the early 1960s.

Anesthetists deal with airways every day, and the expansion of interest to intensive care seemed natural. Initially part-time intensivists and then full-time intensivists, it was a simple and obviously practical extension of skills to prolong the anesthetic into the postoperative period and support the patients with mechanical ventilation following complex surgical procedures. After the resuscitation process, where were the successfully resuscitated patients going to be cared and monitored, and who was going to look after them? In Australia and New Zealand, most ICUs are controlled by anesthetists. The North American ICU involves a much more diverse professional team that includes surgeons, anesthetists and physicians.

REVIEW OF THE LITERATURE: OUTCOME AFTER CARDIOPULMONARY RESUSCITATION

Without a doubt, CPR is one of the most significant interventions conceived to support and restore perfusion and tissue oxygenation in the short-term care of apnea and pulselessness, even though its success preceded the accurate understanding of the physiology of blood flow through the heart under arrested conditions. Its success has been more than just anecdotal. However, as will be seen, this amazingly simple and easily taught systematic procedure should be thought of more as a means of extending the "window of hope of reversing death," until more sophisticated interventions can be instituted, rather than the ultimate therapeutic maneuver.

Out-of-Hospital Cardiopulmonary Resuscitation

Much of the information pertaining to prehospital CPR has come from studies dating back to the early 1970s from Seattle,[27, 28, 144] King County,[124] and Milwaukee[136] in the United States. Discharge survival rates vary from less than 1%[58, 71] to 86%.[24, 139] The accepted factors that seem to influence survival after out-of-hospital cardiac arrest involve the interaction of patient-dependent and resuscitation-dependent factors.[38, 39, 41, 43]

Patient-dependent factors clearly shown to be of importance are intrinsic heart disease, other associated medical conditions, and the presenting cardiac rhythm (ventricular fibrillation as opposed to asystole or electromechanical dissociation). Best results occurs with ventricular fibrillation, with hospital discharge rates as high as 30%. However, even asystole and electromechanical dissociation is associated with an occasional good survivor.[106]

The influence of age alone on survival has been contradictory. It is only in the last few years that a clear trend seems to have been identified. However, factors such as underlying medical condition, pathologic diagnosis, and level of function, reflecting physiologic age rather than chronologic age, are probably as important as age alone. But few studies have specifically looked at the aged population. In 1989, Murphy and coworkers[105] reported, albeit in a retrospective study, cardiac arrest outcome of patients over 69 years of age. Of 244 out-of-hospital cardiac arrests, 2 survived to hospital discharge (both witnessed arrests). Tresch and coworkers[151] in 1988 noted a 16% survival to hospital discharge in a patient group under 70 years of age, compared with 9% survival in those older than 70 years. In 1990, the same group of workers[153] found a 24% survival rate among the younger patients as opposed to 10% for the patients over 70 years of age.

Resuscitation-dependent factors that have been shown to be important are witnessed versus unwitnessed, bystander-initiated CPR, the time from collapse to the initiation of CPR, and the time from the collapse to the arrival of advanced life support interventions such as defibrillation.[12, 37, 40, 62, 104, 135, 139, 167] Some centers in the United States, e.g., Milwaukee, have an amazing average response time from placement of the arrest call of only 21 minutes. This contrasts with an Australian report where the average response time in a major metropolitan area was 15.9 minutes.[130] The recent introduction of the automatic external defibrillator seems to have had an impact if applied early to the arrest victim.[163] Prolonged prehospital CPR (longer than 30 minutes) is associated with poor survival. This also correlates with a poor outcome, as is arrival in the emergency room without a pulse, with survival ranging from 3% to 8%[43] (Table 1).

Eisenberg and coworkers[46] recently reviewed 39 studies published between 1967 and 1988 involving a variety of emergency response systems (Table 2). They compared survival data for the following systems: basic emergency medical technician (EMT); EMT defibrillation (basic EMTs also trained in use of defibrillators); paramedic (trained in advanced cardiac life support and able to provide definitive care, such as defibrillation, intubation, medications); basic EMT/paramedic; and EMT defibrillation/ paramedic system. The first three systems were regarded as single response systems and the latter two systems as double response systems. There was an overall trend in improved survival as the sophistication of the response team increased, most significantly between the single to the double response system, (from 10%–17% for all cardiac arrests; from a range of 6%–26% for the various EMT defibrillation teams, to 11%–33% for the EMT/paramedic programs, for ventricular fibrillation). The current gold standard with the present technology, techniques, equipment, and medications is a 30% hospital discharge rate in Seattle using a double response system.[168]

In Australia, most centers use a single response system, which can vary from the equivalent of the EMT (ambulance, often with defibrillator capabilities) to paramedic response teams in the larger cities. In either case, most teams have defibrillation capabilities. Average available response times for these teams range from 4 to 7 minutes. Australian studies of ambulance resuscitation for ventricular fibrillation are rare. One study had a survival to discharge rate of 21% for ventricular fibrillation, using on-site defibrillation. However, the mean delay before arrival of the paramedics in this study was 15.9 minutes.[130]

Table 1. PREDICTORS OF SUCCESSFUL OUTCOME IN THE ADULT

Out-of-hospital arrest versus in-hospital arrest
Witnessed arrest
Bystander CPR
Short response time to CPR (<5 minutes)
CPR <15 minutes
Respiratory versus cardiac
Presenting rhythm
Two or less doses of adrenaline

On the other hand, if the patient arrives pulseless to the emergency room after out-of-hospital CPR, outcome is uniformly dismal, with an average survival to hospital discharge of only 0.5%. Bonnin and coworkers had one neurologically intact hospital discharge survivor out of 244 adult nontraumatic out-of-hospital cardiac arrests.[14, 48, 80, 89, 135, 157]

Long-term survival is often difficult to interpret from the studies. Five-year survival seems to approximate 50%. Many early deaths occur as a result of recurrent arrhythmias. To prevent sudden cardiac death, survivors must be thoroughly investigated during their initial hospitalization and appropriate follow-up and therapy must be maintained.[16, 30, 42, 56, 150]

Of major relevance when discussing CPR is neurologically intact survival. Neurologic failure generally relates to unwitnessed arrests, failure of initiation of bystander CPR, or prolonged time to arrival of the prehospital resuscitation team. Of those studies recording the neurologic condition of survivors, rates of injury average about 20%, but have been reported to be as high as 60%. Studies of unwitnessed arrests show not only poor survival but also a high incidence of brain damage among the rare survivor. Longstreth and coworkers[94] retrospectively reviewed 459 survivors of out-of-hospital cardiopulmonary arrest, of whom 59% either never awakened or had persistent brain damage of some degree. In the Brain Resuscitation Clinical Trial 1 Study Group,[15] in which 262 comatose survivors of cardiac arrest were studied (three quarters of which were out-of-hospital cardiac arrests), only 18% of the total study population were alive at 12 months, of whom 84% recovered good neurologic function.[1, 15, 30, 35, 37, 87, 94, 131, 152]

In-Hospital Cardiopulmonary Resuscitation

Since the advent of CPR, not only has the technique been refined and reappraised, but most hospitals have responded in a consistent fashion, i.e., by the development of rehearsed emergency code teams to respond to in-hospital cardiac arrests. Standardized training of hospital staff has also been shown to be of value.[96] Unfortunately, these code teams are often unfamiliar with the arrested victim and must initially assume the potential resuscibility for all patients. Initially conceived to "resuscitate a heart too good to die" (i.e., acute reversible illness), CPR has since gained widespread, if not indiscriminate use, for the full spectrum of possible medical conditions (including the aging process).

Survival after a cardiac arrest occurring in the hospital has been unchanged since CPR's inception in 1959 (Table 3). One paper even asked if survival had decreased.[29] However, if one looks at the actual survival rates from the multitude of studies that deal with in-hospital cardiac arrests, it can be seen that there has been minimal overall change in either immediate survival or survival to discharge. However, this contrasts with the increasing complexity of illness and an aging population.

The type of hospital influences frequency of arrest response, effectiveness of resuscitative efforts, and survival. Location of the arrest within hospital has a variable influence on long-term survivability. Witnessed arrests have a higher survival potential than unwitnessed arrests. Resuscitation of some of the unwitnessed arrests are certainly an assault on the dead. Attempted resuscitation longer than 15 minutes is associated with poor outcome. Arrest on the general wards consistently has the least success, whereas emergency room and coronary care unit cardiopulmonary arrests tend to have the highest success

Table 2. PATIENT CHARACTERISTICS AND SURVIVAL FROM OUT-OF-HOSPITAL CARDIAC ARREST

Type of EMS System and Location*	No. of Attempted Resuscitations	Average Age (yr)	% Male Patients	% Witnessed	Average EMT Response Time in Minutes	Average Paramedic Response Time in Minutes	% With Bystander CPR	No. in All Rhythms Discharged (%)	No. in VF (%)	No. in VF Discharged (%)
Basic EMT										
Durham[171]	126			47†	6.5		35†	11 (9)	61 (48)†‡	7 (11)†
Goteborg[67]	189			100				3 (2)†	23 (12)	
Iowa[139]	52	64	69	73	7		31	1 (2)	31 (60)	1 (3)
King County[39, 40]	323	64†	68†	51†	4.3†		91†	19 (6)†	147 (57)†	18 (12)†
Minnesota[5]	118		79†	100			37†	3 (3)		
Reykjavik[60]	222	63	75†		7.3			21 (9)		
Vancouver[159]	110						16†	6 (6)†	90 (41)†	18 (20)
Winnipeg[154]	849							33 (4)	226 (27)‡	24 (11)
EMT-D										
Iowa[139]	110	68	75	70	5.7		20	12 (11)	64 (58)	12 (19)
King County[40]	54	62	89	79	4.3		22	10 (19)	38 (70)	10 (26)
Minnesota[163]	100	70	73†	70	10 (84%)		50†	6 (6)	51 (51)	6 (12)
Stockholm[70]	307							11 (4)†	144 (47)†‡	9 (6)†
Stockport[58]	103							15 (15)	70 (68)	15 (21)
Paramedic										
Auckland[26]	405		75				55	72 (18)†		
Brighton[98]	356							39 (11)		
Charleston[100]	100	56	72†			7	19	7 (7)		
Cincinnati[84]	147		74†					22 (15)		
Israel[44]	2,995	68	71	82		6	8	210 (7)	839 (28)	126 (15)

Los Angeles[62]	300	65	68	41		5	35†	30 (10)	135 (45)	19 (14)
Lucas/Kent[55]	2,171					4.7		169 (8)		
Miami[91]	301	63	75			4 (80%)			301 (100)	42 (14)†
Minnesota[5]	46		80†	100			48†	5 (11)	26 (57)	5 (19)
N Westminster[159]	227							21 (9)†	116 (51)†	15 (13)†
Oregon[122]	210							38 (18)†		
Pittsburgh[124]	187	68†				6	19†	18 (10)†	98 (52)†‡	15 (15)
Tampa[4]	296	58				5 (87%)			296 (100)	68 (23)
Torrance[32]	120		82†			4 (70%)		16 (13)	50 (42)†	15 (30)†
EMT/Paramedic										
Columbus[90]	129				3	5		32 (25)		
Durham[115]	168				6.5§	8.7		7 (4)		
Goteborg[67]	176					5		19 (11)	87 (49)†	
King County[27]	1,297	65†	78†	100	4.4	9.1†	45†	344 (26)†	947 (73)†	312 (33)
Milwaukee[136]	1,905			100	2	5	31†	303 (16)	779 (52)†‖	183 (23)
Minneapolis[119]	514							83 (16)		
New S Wales[130]	434			55†			30	91 (21)	369 (85)	81 (22)
Seattle[160]	725			67	3	6.5§	40		725 (100)	181 (25)
Vancouver[158]	244						12†	28 (11)†		. . . (24)
York Adams[47]	1,066	67	69	79				68 (6)†	454 (43)†	51 (11)†
EMT-D/Paramedic										
Seattle[168]	687	65	81	79	3.6	8.8	36	98 (14)†	276 (40)	83 (30)
King County[45]	4,068	66	75	55	4.2	10	54	741 (18)	2,117 (52)	615 (29)

*EMT = emergency medical technician; EMT-D = emergency medical technician-defibrillation.

†Calculated from available data.

‡Includes VF and ventricular tachycardia.

§Estimated from available data.

‖Includes coarse VF only.

From Eisenberg MS, Horwood BT, Cummins RO, et al: Cardiac arrest and resuscitation: A tale of 29 cities. Ann Emerg Med 19:179, 1990; with permission.

Table 3. SURVIVAL AFTER A CARDIAC ARREST OCCURRING IN THE HOSPITAL

Author	Reference	Year Published	Total No. of Patients	Short-Term Survivors (%)	Long-Term Survivors (%)
Jude	75	1961	118	—	28 (24)
Klassen	82	1963	126	42 (33)	17 (14)
Jordan	74	1964	100	—	3 (3)
Greenfield	59	1964	360	—	10 (3)
Kaplan	77	1964	100	29 (29)	6 (6)
Lawrence	85	1964	111	41 (37)	15 (14)
Smith	134	1965	128	38 (30)	23 (18)
Lillihei	92	1965	200	100 (50)	33 (16)
Stemmler	137	1965	103	13 (13)	5 (5)
Grace	57	1966	108	24 (22)	15 (14)
Kirby	81	1967	100	47 (47)	22 (22)
Linko	93	1967	100	49 (49)	27 (27)
Johnson	73	1967	298	95 (32)	42 (14)
Ho	65	1967	119	48 (40)	20 (17)
Jung	76	1968	100	46 (46)	20 (20)
Saphir	132	1968	123	—	10 (8)
Hubbell	69	1969	104	—	18 (17)
Minuck	103	1969	293	116 (40)	27 (9)
Hollingsworth	66	1969	368	91 (25)	30 (8)
Dupont	33	1969	161	95 (59)	38 (23)
Jeresaty	72	1969	237	106 (49)	52 (22)
Peschin	114	1970	734	315 (42)	28 (4)
Volastro	161	1970	512	219 (43)	64 (12)
Brown	17	1970	184	88 (48)	18 (10)
Stiles	138	1971	302	—	44 (15)
Camarata	21	1971	132	50 (38)	6 (5)
Lemire	86	1972	652	—	148 (23)
Farha	50	1972	347	115 (33)	38 (11)
Kaunitz	78	1972	127	46 (36)	26 (17)
Wildsmith	169	1972	537	135 (25)	64 (12)
Dykema	34	1973	212	68 (32)	31 (15)
Castagna	22	1974	137	48 (55)	14 (10)
Fabricius-Bierre	49	1974	209	66 (32)	25 (12)
Vijay	160	1975	150	38 (17)	13 (9)
Messert	102	1976	183	48 (26)	28 (15)
Peatfield	113	1977	1063	345 (32)	93 (9)
Fusgen	52	1978	335	—	24 (7)
Hahn	63	1979	128	67 (52)	24 (19)
Coskey	25	1978	1155	475 (41)	277 (24)
Tweed	154, 155	1980	1187	617 (52)	204 (17)
DeBard	31	1981	1073	615 (57)	223 (24)
Bedell	8	1983	294	128 (44)	41 (14)
Suljaga-Pechtel	140	1984	207	137 (49)	21 (10)
McGrath	99	1987	268	97 (36)	37 (14)
Taffet	141	1988	329	161 (48)	22 (6)
Murphy	105	1989	503	112 (22)	19 (4)
Timerman	145	1989	536	252 (47)	43 (8)
Burns	19	1989	122	56 (46)	9 (7)
Tortolani	149	1989	123	28 (23)	12 (10)
George	53	1989	140	75 (55)	29 (21)
Roberts	118	1990	310	115 (37)	30 (9.7)

rates. CPR results when performed on patients in an ICU varies with the type of ICU and severity of illness of the patient, with long-term survival rates between 4% and 20%. Immediate success rates average about 50%. Overall survival to discharge ranges between 7% and 20%.[8, 19, 31, 64, 131, 140, 141, 145, 156]

Underlying cardiorespiratory disease is by far the most common condition precipitating cardiac arrest in the in-hospital population. There is a reduced incidence of ventricular fibrillation, and an increased incidence of asystole and electromechanical dissociation as the precipitating arrhythmia. Patients with ventricular fibrillation and ventricular tachycardia continue to have better survival rate than those with asystole or electromechanical dissociation, but Tortolani and coworkers[149] report a survival rate of 10.6% for asystole. This is a far from hopeless result. Isolated respiratory arrest is rarely addressed, but it seems that resuscibility is less in the adult as compared with the pediatric patient (see the following discussion).

The sicker the patient before the arrest, the less chance of survival. The study by Bedell et al[8] in 1983 was one of the first to highlight the significant influence that preexisting underlying disease, be it acute or chronic, affects outcome of cardiopulmonary arrest in the hospital. In their study, patients with pneumonia, renal failure, cancer, hypotension, and homebound lifestyle were unlikely to survive a cardiac arrest. Taffet et al[141] in 1988 observed that witnessed arrest in patients aged less than 70 years was associated with live discharge, whereas the presence of cancer and sepsis was associated with poor outcome. Roberts and coworkers[118] in Manitoba confirm dismal although not hopeless prognosis in patients with severe underlying illness. Another recent study confirmed the detrimental effect of underlying illness on long-term survivability of in-hospital CPR.[53]

Age was not a significant influencing factor in the studies by Bedel et al[8] and Roberts et al.[118] In contrast, in the retrospective study by Murphy et al[105] in patients over the age of 69 years, 15 of 204 witnessed in-hospital arrest patients were discharged, and 1 of 116 unwitnessed in-hospital arrest patients was discharged. Taffet et al[141] had similarly discouraging results in the elderly patient population (Table 4).

Few papers specifically discuss long-term neurologic follow-up, but generally use the nonspecific term "long-term survival." In the few papers that do discuss neurologic outcome, a range of 93% to 99% good recovery is reported. More sobering, in the study by Murphy et al,[105] the only survivor of 237 elderly patients with asystole, electromechanical dissociative (EMD), or agonal rhythm was discharged in a persistent vegetative state. Absolute numbers of impaired survivors are low. However, Levy and coworkers[87] noted a 13% good outcome in a group of 210 patients in coma for at least 6 hours, who had suffered a hypoxic-ischemic cerebral insult in a variety of locations, both in and out of the hospital.

Table 4. HOSPITAL CARDIOPULMONARY RESUSCITATION AND THE ELDERLY

	(% Survivors at Discharge)	
Source	**< 70 Yr**	**> 70 Yr**
Murphy et al, Boston, 1989[105]	—	6.5
Taffet et al, Houston, 1988[141]	16	0
Bedell et al, Boston, 1983[8]	15.4	10.4
Gulati et al, 1983[61]	18.2	17.1

Table 5. PEDIATRIC CARDIAC ARREST

Author	Year	Location	Number of Cardiac Arrests	% Survival
Gillis et al[54]	1973	Toronto	55	11
Eisenberg et al[43]	1983	Washington	119	7
Lewis et al[88]	1983	Milwaukee	58	15
Torphy and Minter[148]	1984	Milwaukee	91	6
Rosenberg[123]	1984	Michigan	26	15
O'Rourke[112]	1986	Boston	34	21
Gillis et al[54]	1986	Toronto	33	9
Nichols et al[108]	1986	Philadelphia	36	25
Zaritsky et al[172]	1987	Washington, DC	53	9
Thompson et al[143]	1990	Wisconsin	70	4

PEDIATRIC CARDIOPULMONARY RESUSCITATION

The pediatric population is anatomically and physiologically distinct. A common misconception is that children survive cardiorespiratory arrests better than adults. Two earlier studies[36, 165] suggested that between 40% and 50% of children suffering a cardiorespiratory arrest in the hospital survive to leave the hospital. These studies combined the results of pure respiratory arrest with cardiac arrest cases. It is much more useful to distinguish a pure respiratory arrest from a cardiorespiratory arrest[43, 54, 108, 112, 143, 148, 162, 172] (Tables 5 and 6). As one might expect, survival following a respiratory arrest is much better than that following a cardiac arrest in the pediatric patient.

Most cardiac arrests in children occur in those less than 2 years of age. The epidemiology of cardiorespiratory arrest differs from that of the adult population (Tables 7 and 8). The majority of cardiac arrests in pediatric patients occur as a result of hypoxemia, followed by a secondary bradycardia or asystole. This is in contrast to the primary arrhythmias (especially ventricular fibrillation and asystole) of adults. Predictors of successful outcome are shown in Table 9.

Neurologic outcome following a cardiac arrest in a child seems to be much worse than in the adult studies. In- and out-of-hospital cardiac arrests have similarly dismal recovery rates, with neurologic impairment rates among survivors of between 35% and 100%.[88, 112, 121] This is presumably related to delayed recognition of hypoxemia, allowing the onset of asystole, which universally has a dismal prognosis, be it a primary or a secondary arrhythmia, i.e., a prolonged prodrome prearrest scenario. Recovery from a pure respiratory arrest is much more encouraging because less severe hypoxemic insult is expected. Few studies address this issue specifically. Thompson and

Table 6. PEDIATRIC RESPIRATORY ARREST

Author	Year	Location	Number of Respiratory Arrests	% Survival
Gillis et al[54]	1973	Toronto	7	86
Lewis et al[88]	1983	Milwaukee	16	75
Gillis et al[54]	1986	Toronto	9	44
Nichols et al[108]	1986	Philadelphia	9	88
Zaritsky et al[172]	1987	Washington, DC	40	67.5
Thompson et al[143]	1990	Wisconsin	25	84

Table 7. EPIDEMIOLOGY OF PEDIATRIC OUT-OF-HOSPITAL CARDIAC ARREST

Age: 45%–60% <1 year
Underlying disease: uncommon
Most common rhythm: asystole
Etiology:
  Sudden infant death syndrome
  Trauma (drowning, road trauma)
  Respiratory (especially airway)
  Congenital cardiac lesions

coworkers[143] reported an intact survival rate after pure respiratory arrest of 88%. The etiology of the respiratory arrest also has a bearing on outcome.

NEONATAL CARDIOPULMONARY RESUSCITATION

Birth asphyxia is a common and often unexpected event. Aggressive resuscitation seems warranted as sequelae range from 7% to 22%, with a mortality of 20% to 50% for an Apgar score of 0 to 3 at 5 minutes.[74a] Premature neonates suffer a poor outcome after cardiorespiratory arrest. Indeed, one author was driven to comment that CPR should be regarded as experimental in this population.[83, 170]

TRAUMA AND CARDIOPULMONARY RESUSCITATION

The well-documented benefits of CPR following sudden collapse with ventricular fibrillation have not been demonstrated in the trauma patient who arrives in the emergency room pulseless. Long-term survival after blunt trauma causing cardiac arrest ranges from 0% to 12.3% when confined to patients

Table 8. EPIDEMIOLOGY OF PEDIATRIC IN-HOSPITAL CARDIAC ARREST

Age: 60% <2 years
Underlying disease: common (>80%)
Most common rhythm: asystole
Etiology:
  Cardiovascular disease
  Respiratory disease
  Sepsis
  CNS disease
  Congenital malformations

Table 9. PREDICTORS OF SUCCESSFUL OUTCOME IN PEDIATRIC PATIENTS

In-hospital versus out-of-hospital arrest
No underlying chronic illness
Short response time to CPR (<5 minutes)
CPR <15 minutes
Respiratory versus cardiac arrest
Two or less doses of adrenaline

presenting with pulselessness. Long-term survival after penetrating injury ranges from 0% to 46% following open thoracotomy and open cardiac massage.[68, 133] It has been demonstrated experimentally that cardiac output from external cardiac massage is negligible in the hypovolemic cardiac arrest setting.[97] Aggressive trauma room intervention of cardiac arrest or the pulseless state has been encouraged in many American centers. Yet the survival results from trauma room thoracotomy and open cardiac massage are far from impressive. Both adult and pediatric patients have a uniformly hopeless outcome if arriving in the emergency department in a pulseless state after sustaining blunt chest trauma.[125] Patients who have sustained severe blunt trauma and arrive in the emergency room pulseless should be declared "dead on arrival." CPR in this setting should also be regarded as experimental.

NEAR DROWNING

Survival following an immersion is dependent on the following clear factors: short submersion time and bystander-initiated CPR. Most of the remarkable anecdotal reports of intact recovery of near drowning have occurred after cold water immersion. There are also many case reports of neurologically intact survivors of prolonged immersion and prolonged resuscitation. If one examines those patients who arrive in the emergency room with absent respirations and absent pulse, intact survival is almost universally dismal.[9] A recent paper by Quan and coworkers[116] from Seattle claimed a 32% survival rate from cardiopulmonary arrest following submersion of a pediatric patient, with 67% of survivors unimpaired or mildly impaired. A closer look reveals that there was only one completely normal recovery from 12 cardiopulmonary arrests, and no survivors in those children arriving without a pulse. Predictors of hopelessness were CPR duration of greater than 25 minutes and submersion duration of greater than 25 minutes. The child that arrives conscious to the hospital in most cases will do well, unless complications intervene, such as the adult respiratory distress syndrome.

Among survivors of near drowned children, neurologic injury is common. If one considers all survivors, neurologic sequelae range from 0% to 30%. If one considers patients arriving in the emergency department without a pulse or admitted to the ICU with a Glasgow Coma Scale of 3, sequelae among the rare survivor range from 60% to 100%.[2, 51, 109, 110, 111, 116] ICU cerebral resuscitation protocols have not been shown to be of any benefit to improved cerebral recovery.[13]

ANESTHESIA AND CARDIOPULMONARY RESUSCITATION

The incidence of cardiac arrest related to anesthesia in Australia has been difficult to document accurately because of the voluntary nature of the reporting procedure for this complication. In only one state, Western Australia, is reporting of anesthetic-related deaths mandatory. Despite these problems, the National Health and Medical Research Council published a report in 1990 on anesthetic-related mortality for 1985 to 1987. From the available information, there were 153 anesthetic-attributed deaths, from a minimum of 5.47 million delivered anesthetics for the triennium, representing a minimum anesthetic mortality of 2.8 per 100,000 anesthetics given. There was only one death in the age group 0 to 10 years. There is no information with regard to total numbers of cardiac arrests or their resuscibility.[107]

In a Canadian study, incidences of cardiac arrest ranged from 7.8 per 10,000 anesthetics in the operating room and 3.5 per 10,000 in the recovery room.[23] In the United States, anesthesia has been estimated to be the sole cause of death for 1 in 10,000 cases.[78] In the UK, anesthesia was thought to be the sole cause of death in 0.1% of perioperative deaths.[18] The major risk factors in most reports seems to be the pediatric and elderly populations and emergency surgery. Because of the location of the arrest, successful resuscitation from a cardiac arrest related to anesthesia could be expected to be higher than in other hospital locations. Keenan and Boyan[79] reported a survival at 78%, with 48% of the resuscitated patients discharged alive from the hospital, all but one with intact neurologic function. However, in a large multicenter study from France,[146] there was only a 36% survival from 59 cardiac arrests in 198,103 anesthetics. Almost half of the perioperative cardiac arrests occur in the postoperative period. The most common causes of cardiac arrest and death related to anesthesia are listed in Table 10.

IS THERE ANY HOPE?

The current accepted gold standard for survival after out-of-hospital cardiac arrest is about 30%; for in-hospital cardiac arrest, it is about 25%. The development of alternatives to standard CPR, such as simultaneous chest compression and ventilation, static pneumatic external couterpulsation, high-impulse, rapid-rate chest compressions, and interposed abdominal binding and compression, have increased our understanding of the mechanisms of blood flow during CPR, rather than improved survival. Survival after a cardiac arrest is determined by both the extent of cerebral injury and other vital organ injury. In some cases of cardiac arrest, survival has been limited not by the neurologic injury, but by such complications as aspiration pneumonitis. As a result of the total body insult, there are a number of potentially detrimental circulating mediators of further injury, such as endotoxin and the cytokines. Do these mediators contribute directly or indirectly to the ongoing neurologic injury?

Our ability to support multiorgan failure over the last decade has been based on an increased understanding of the pathophysiologic evolution of injury and repair, as well as by many new technologic interventions. Laboratory studies have shown that the pathophysiologic processes influencing eventual neurologic outcome continue during the postischemic period for many hours to days. For there to be any improvement in survival following a cardiac arrest,

Table 10. MOST COMMON CAUSES OF ANESTHETIC-RELATED DEATHS

Drug overdose
Inadequate ventilation/failed intubation
Acid aspiration
Airway obstruction
Anaphylaxis
Cardiac failure
Cardiogenic shock
Cerebral hypoxia
Halothane-related hepatic failure
Intravenous injection of local anesthetic
Malignant hyperpyrexia
Lack of experience/care/knowledge

techniques to prevent or reverse the currently known sequence of events will need to be discovered. To date, our understanding of the pathophysiologic sequence of cerebral injury outstrips our ability to intervene successfully.

There are simultaneous circulatory and metabolic changes occurring after the restoration of blood flow after global cerebral ischemia. Immediately after reperfusion there is a period of increased cerebral blood flow, followed by a period of prolonged reduction in cerebral blood flow to less than preischemia levels, despite maintaining an adequate perfusion pressure. The cerebral metabolic rate of oxygen is also depressed and remains depressed even after the normalization of cerebral blood flow. The "no-reflow" phenomenon refers to the failure of reestablishment of regional cerebral circulation. Is this a result of a vasospastic state, endothelial and glial cell damage and swelling, intravascular coagulation, or some other as yet unexplained mechanism?

What are the biochemical derangements that are known to occur during and after ischemia? There seems to be a final common pathway for injury no matter what the organ. Some of these steps are injurious in themselves. Some are activation steps, requiring the presence of oxygen delivered during the reperfusion stage to render the full extent of injury capabilities.

Following the onset of the ischemic insult energy stores are exhausted after only 3 to 4 minutes. This appears not to be an irreversible problem resulting in irreversible cell injury. Membrane depolarization occurs spontaneously as a result of the energy depletion, initiating ion fluxes. Two well-described ion fluxes that are known to occur are those of potassium and calcium. Potassium leaks to the extracellular space as sodium moves to the intracellular space, followed by water, resulting in glial and astrocyte swelling, altering intercapillary and intracapillary architecture. The increased extracellular potassium concentration is followed by a marked influx of calcium. As a result a number of detrimental events are initiated. Membrane-bound phospholipase A_2 is activated, with a consequent membrane destruction as well as release of free fatty acids, especially arachidonic acid, which builds up in the cytosol. Xanthine dehydrogenase is converted to xanthine oxidase. Uncontrolled activation of nuclease probably occurs, resulting in DNA injury. An enhanced release of excitatory neurotransmittors (glutamate and aspartate, and maybe others) occurs and have been implicated as mediators of neuronal injury.

On restoration of blood flow the stage of the so-called reperfusion injury begins with the delivery of oxygen. Superoxide and other free radical formation ensues, enhanced by xanthine oxidase, which has built up during the ischemia. The free radicals have both direct and indirect injurious effects on membrane structure, mitochondria, and DNA. Arachidonic acid in the cytosol is a substrate for the cyclo-oxygenase and lipo-oxygenase pathways. These enzyme systems probably become activated on the restoration of circulation and delivery of oxygen, and the production of myriad extremely vasoactive and metabolically active prostaglandins begins, with potential local and systemic effects.

Another reperfusion phenomenon is free iron release. Lipid peroxidation, which involves disturbances of the double bond structure of lipids, requires a transitional metal to act as an inorganic catalyst. Superoxide anion is known to promote iron delocalization from ferritin. Lipid peroxidation causes widespread damage to many of the cell components, from the cell membrane itself to the nuclear membrane, polyribosome and endoplasmic reticulum, lysosomal disruption, and so forth.

The local and systemic disruptive effects of the severe mixed respiratory and metabolic acidosis that occurs secondary to circulatory standstill include enzyme and membrane pump inhibition, mitochondrial inactivation, and lysosomal activation or disruption. High blood glucose levels during and after resuscitation have been demonstrated to experimentally worsen the injury, probably as a result of increased lactate production and accumulation.[20, 95] A more detailed description of the pathophysiology of injury can be found in a number of recent reviews on the subject,[11, 121, 128, 142] as well as elsewhere in this issue.

THE FUTURE

So what can we do in 1992 to improve survival after a cardiac arrest? With our present level of knowledge, at best we can try and extend the therapeutic window for survival until our currently accepted advanced life techniques can be applied. The extension of this window is presently done with a minimum of sophistication. No one could call CPR a sophisticated medical intervention. Some investigators are advocating a return to a more widespread use of open chest cardiac massage. Greater levels of sophistication over the present system are possible in some settings. Cardiopulmonary bypass has been used during acute resuscitation from cardiac arrest, but this technique is obviously going to be confined to the inpatient and to major medical institutions, as well as being limited by cost and technical expertise.[129] The possibility remains that the outcome of extending the therapeutic window will be a greater number of neurologically impaired survivors, in patients whose "hearts were too young to die." If there is an increased survival, how can these survivors be guaranteed a normal neurologic recovery?

Improved outcome will be achieved via a three pronged attack. Greater grass roots education of basic CPR is still the easiest and most economical way of improving current long-term survival results. Most studies that have looked at the influence of bystander CPR on long-term survival have shown a direct correlation of benefit. An added benefit would be the more widespread ability of members of the community to clear obstructed airways of victims of near drowning, road trauma, and foreign body inhalation. However, bystander CPR during out-of-hospital cardiac arrests occurs in only about 10% to 50% of arrests. This is not always related to whether or not the arrest was witnessed, because looking at the available data reveals a large discrepancy of those arrests witnessed versus those who have received bystander CPR.

It has also been shown that the best results occur on early application of advanced cardiac life support. However, this begins to get expensive. All ambulance and paramedic responders should have a defibrillator immediately available. Widespread availability of automatic external defibrillators in public settings should improve immediate resuscibility from ventricular fibrillation. Would the availability of external pacemakers with defibrillators improve resuscibility of cardiac arrest, especially those patients with asystole and electromechanical dissociation? It is very hard to separate individual maneuvers of out-of-hospital resuscitation performed by a paramedic. Those teams that are trained in endotracheal intubation and ventilation as well as defibrillation as part of a well-rehearsed protocol have the best results. More recently, the laryngeal mask airway has become more readily available. These devices require minimal skill and training for their correct insertion, with a minimum of extra equipment required. Would the widespread distribution of these devices to ambulance and paramedic teams assist in the earlier and more effective administration of oxygen and manual ventilation? Not only should the lay community become more aware, but so too should physician training be regularly updated and skills tested.

Our present intensive therapy regimes are effective only in preventing a secondary neurologic insult. Optimal neurologic outcome requires meticulous attention to both intracranial and extracranial homeostasis. This includes optimizing cardiorespiratory support and oxygen delivery after restoration of the circulation, as well as maintaining a normal extracellular fluid and electrolyte milieu. Control of the intracranial pressure has not been shown to be beneficial. At present, any pharmacologic intervention aimed at improving overall survival has been fruitless, except in the animal laboratory. Our present knowledge of the pathophysiology has allowed various site-specific agents to be tested, both in animal and human subjects. The earliest agents to have been discredited were the barbiturates.[15] Present areas of intense research involve agents such as calcium antagonists, free radical scavengers, excitatory amino acid antagonists, anticonvulsants, modulators of prostaglandin activity, iron-chelating agents, and agents directed at minimizing the metabolic acidosis of ischemia, such as dichloroacetate.[10, 120, 121, 128, 142]

The problem with many experimental animal therapeutic studies rests in their unrealistic nature, i.e., many studies have been performed by administering the agent before the onset of ischemia, the ischemic event is the result of some barbaric circulatory occlusion device or the arrest is induced with electric shock or high-dose potassium infusion. In other words, they do not replicate the human clinical reality. Much of research to date has aimed at demonstrating that a stable cardiovascular state can be restored after prolonged cardiopulmonary arrest, without demonstrating long-term survival benefit. Despite the present dearth of useful therapeutic pharmacologic interventions to restore a pulse and reverse neuronal injury, we are at present just skimming the surface of an enormous untapped realm. If we reflect on the remarkable achievements of 30 short years, one can only speculate that with present and future levels of technology the next 30 years will deliver results of which we can only dream.

SHOULD WE RESUSCITATE? WHOM SHOULD WE RESUSCITATE?

The answer to the first question should by now be obvious. Countless lives have been saved by the relatively simple technique of external chest compressions and expired air resuscitation. The second question is somewhat more cumbersome. Despite many clinical situations where long-term outcome after CPR is poor, there are few patient groups or situations where the absolute result is hopeless.

Many unfortunate resuscitations could be avoided with a timely do not resuscitate order (DNR). But who should have DNR orders written? When is the attempt to sustain life absolutely futile? Does not every human with a normal state of mind deserve a last chance of survival? Even though the cost of medical intervention is presently on every medical practitioner's mind, what is the cost, or value, of a normal neurologically intact "life after death." Are we compromising our patients because of governmental restraints on health budgets while defense budget expenditure remains unchallenged? Three accepted principles when considering the resuscibility of a particular patient are quality of life before the arrest, quality of life anticipated after the arrest, and whether CPR is deemed to be medically inappropriate treatment. At present, I would argue for each case to be dealt with according to its own merits.[6, 101, 147] These ethical questions are beyond the scope of this discussion. However, I will attempt to summarize and suggest patient groups in whom, perhaps, CPR should be abandoned.

All patients whose collapses are witnessed should be resuscitated. Resuscitation of the unwitnessed arrest is still successful in up to 5% of cases, similar to that group of out-of-hospital arrests not receiving bystander CPR.[104] Patients retrieved from the scene of trauma and arriving in the emergency department pulseless have a uniformly hopeless prognosis.

But what about patients in the hospital with severe acute underlying illness? The report by Bedell et al in 1983[8] was the first to show that resuscitation of critically ill patients had little chance of success. Several papers have since been published that agree in principle, but no factor has been found to be absolute.[53, 118, 126, 140] There are many variables involved in the ultimate determination of successful outcome in the individual case. In the papers reporting 100% mortality for a variety of acute severe illnesses, the absolute numbers have been small. Patients with the same conditions in another center have been successfully resuscitated. However, conditions in which resuscitation is rarely successful are advanced disseminated malignancy, refractory shock, complicated myocardial infarction, chronic renal failure, and patients in a coma.

Patients with acquired immunodeficiency syndrome (AIDS) suffer from an emotional prejudice with regard to resuscitation from the community and medical profession. Many of the diseases contracted by the AIDS victim early in the disease course can be effectively treated. Physicians attitudes toward in-hospital resuscitation and underlying illness are of interest. For underlying illnesses with similar long-term outlook, more DNR orders were written for patients with AIDS and lung cancer as compared with patients with liver cirrhosis or congestive heart failure.[164] However, a recent prospective study looking at CPR in the AIDS population reported only one long-term survivor of 43 patients with AIDS who underwent CPR.[117]

The increasingly aging population in the western societies is making its impact with the ever-increasing number of studies featuring the elderly. Recent papers would suggest that CPR in this population is futile. At the same time, surgeons are operating on a gradually increasingly older population, with only slightly increased perioperative risks as compared with their younger cohorts. An elderly patient of any chronologic age, if in good physiologic condition, deserves serious consideration to aggressive resuscitation if the situation were to arise during the hospitalization. The issue needs discussion with the patient before the event arises so that an intelligent and mutual intercourse on quality of life and expectations can occur, allowing the right decision to be made for that patient, based on the patients underlying health and acute illness, and the medical facts as they stand today. Out-of-hospital resuscitation of the elderly is dismal. The bedridden elderly patient also has an almost hopeless outlook.

Considerations and decision making with the pediatric patient is often more emotional than cerebral. Results of CPR in the pediatric population are poor. But are there any specific patient groups that an attempt to resuscitate should not be made? Some centers report zero good survivors among children who arrive in the emergency room pulseless.[111] Others have reported 20% survival in near drowned children arriving in the emergency room without a pulse[110, 115] whereas other centers report that all survivors of resuscitation in the emergency room, from a cardiac arrest after a near drowning accident, are neurologically impaired. Where do we draw the line? Neonates less than 600 g can have a good survival in specialist neonatal centers, but should they undergo CPR in the event of a cardiac arrest? Children with some chromosomal or degenerative neurologic and neuromuscular disorders have a limited lifespan at the best. Pediatricians caring for children with these terminal conditions need to be more realistic, in order that the truth is conveyed to inform and educate the parents regarding the realities of CPR in their child, instead of generating clouds of emotional confusion.

WHAT IS OUR ROLE IN THE FUTURE?

Anesthetists and critical care specialists have a vital role to play in the future of cardiopulmonary cerebral resusitation. They are ideally placed within the world of medicine to contribute to the ongoing evolution of CPR. Present and future areas of involvement of these specialties include the following:

1. their proximity and expertise in recognizing and managing airway and respiratory compromise,
2. their skills in fluid resuscitation of the various shock states,
3. broad-based medical knowledge,
4. broad-based pharmacologic knowledge,
5. education of medical and surgical interns and residents as well as the ambulance and paramedic personnel in airway and resuscitation skills,
6. refinements of current resuscitation techniques,
7. ongoing research into the preservation and reversibility of cerebral and other major organ ischemic injury,
8. development of animal and human clinical trials that reflect the actual human clinical cardiac arrest scenario.

Today's concepts are tomorrow's realities. Our present level of understanding of the pathophysiology of hypoxic-ischemic injury will act as a platform on which these ideas bear fruition in the form of effective therapeutic measures that will either prolong the window of opportunity or reverse the cellular changes that are today irreversible. The groundwork is being laid today. Tomorrow's technologic improvements can only be awaited with anticipation: if the past 30 years were any indication, the next 30 years will indeed be exciting.

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PREOPERATIVE ASSESSMENT OF NEUROLOGIC FUNCTION IN THE NEUROSURGICAL PATIENT

K. A. Brown, MD, FRCP(C)

This century has witnessed exciting advances in the preoperative assessment of the neurosurgical patient because of both an increased understanding of cerebral pathophysiology and improved diagnostic imaging techniques. The complexity of the diagnostic work-up is determined by the nature of the clinical presentation. This review focuses on those aspects of the preoperative assessment of cerebral function that are important to the anesthetic management of the neurosurgical patient.

The cornerstone of the assessment of cerebral function rests on the history and physical findings of the clinical presentation. The preoperative anesthetic work-up of the neurosurgical patient requires (1) an assessment of intracranial pressure (ICP), (2) an assessment of the function of vital respiratory and cardiovascular centers in the brain stem and spinal cord, and (3) an assessment of the specific disturbance in neurologic function.

The patient with intracranial hypertension, presenting for neurosurgical evaluation, encompasses such diverse conditions as intracranial hemorrhage, hydrocephalus, shunt malfunction, or craniosynostosis. These different pathologies have in common an intracranial volume of blood, brain, tumor, edema, and cerebrospinal fluid (CSF), which results in excessive ICP.

Patients with increased ICP may present with one of two distinct clinical pictures: (1) a critical reduction of cerebral blood flow or (2) herniation of intracranial contents.

Cerebral blood flow (CBF) is determined by the ICP and the cerebral perfusion pressure. ICP is age dependent. In children under the age of 8 years, ICP is less than 7 mm Hg, whereas in adults it is normally between 10 and 15

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mm Hg. Cerebral perfusion pressure is largely determined by blood pressure, which is also age dependent. Given a normal blood pressure, cessation of diastolic blood flow may occur around an ICP of 15 mm Hg in an infant, whereas an ICP in excess of 30 mm Hg is required in older children. A critical decrease in CBF may result in ischemic injury, especially in the watershed areas between adjacent arterial supplies.[25, 44]

The clinical presentation of the patient with intracranial hypertension varies with the time course of the increase in ICP. Sudden massive increases in ICP may present with coma. In subacute presentations a history of a headache on awakening, presumably related to the hypercarbia accompanying sleep, and associated with and relieved by vomiting is common. Children may show increased irritability or a personality change. Infants may have delayed developmental milestones.[4]

Physical findings of intracranial hypertension also depend on the age of presentation and the site of obstruction to the flow of CSF. Intracranial hypertension in infants presents as hydrocephalus and is associated with a disproportionate increase in head circumference, a bulging anterior fontanelle, and dilated scalp veins. In older children visual tracking deficits due to oculomotor or gaze palsies may occur. Injury to cranial nerve III may result in ptosis. Injury to cranial nerve VI produces a squint from a loss of abduction. Papilloedema and absent venous pulsation of the retinal vessels may be present.[4, 25, 44, 45, 48, 49]

Shifts of intracranial contents occur when asymmetrical increases in pressure create pressure gradients across (1) the falx, (2) the tentorium, or (3) the foramen magnum, which result in herniation of brain contents.

An asymmetrical increase in supratentorial pressure may cause herniation of brain across the free edge of the falx or through the incisura of the tentorial notch. Tentorial herniation (uncal syndrome) results in typical eye and motor signs as the diencephalon moves backward through the tentorial notch. Compression of the superior colliculus results in the vertical gaze palsy (sunset sign) distinguished by forced downward deviation of the eyes. Compression of the oculomotor center results in a dilated and unreactive pupil and is a sign of life-threatening brain stem compression. Compression of the posterior cerebral artery against the tentorium results in hemianopia. Calcarine infarction may arise from bilateral posterior cerebral artery compression and may lead to irreversible blindness.[4, 37]

Motor signs associated with tentorial herniation may arise. Compression of the cerebral peduncle against the tentorium may cause hemiplegia. Midbrain compression in children is associated with (1) extensor hypertonus in the arms and legs (doggy paddling arms and cycling legs), (2) opisithonus, (3) decerebrate rigidity, (4) decorticate posturing, and (5) hypotonia. Further compression of the midbrain results in coma, hypertension, bradycardia, tachypnea, and periodic respirations. As pressure in the medullary respiratory center increases, bradypnea occurs followed by apnea. Respiratory arrhythmias may occur.[4, 25, 37]

In contrast, intracranial hypertension from infratentorial lesions may lead to herniation of the cerebellum downward through the foramen magnum or upward through the tentorium. Herniation of the brain out of the posterior fossa is associated with oculomotor signs, vomiting, and cranial nerve abnormalities. Loss of upward gaze (sunset sign), miotic fixed pupils, and central hyperventilation are suggestive of posterior fossa hypertension. Failure of vocal cord abduction may result in inspiratory stridor. Rarely, upward herniation of the brain stem may be associated with proptosis if obstruction of the vein of Galen occurs.[4, 25, 37]

In addition to the baseline value of pressure, the ICP waveform is also useful in assessing ICP. Physiologic waveforms are associated with changes in arterial pressure and central venous pressure. Autoregulation normally serves to dampen the physiologic fluctuations. However, if autoregulation is lost this pulse-wave pressure becomes evident and may approach the systolic/diastolic pressure gradient.[25]

The normal compliance of the intracranial contents is described by a sigmoid-shaped curve. As the volume of intracranial contents increases, the compliance decreases. In infants with elevated ICP, pulsations synchronous with the pulse pressure may be palpable through the fontanelle. Pathologic ICP waveforms are identified as plateau A waves, B waves, and C waves. Plateau A waves are of high amplitude (50–100 mm Hg) and long duration (5–20 minutes) and represent a failure of autoregulation. B waves (< 50 mm Hg) are of brief duration and indicate brain stem failure. C waves (< 20 mm Hg) occur four to eight times a minute and may be an exaggeration of the normal fluctuation in systemic blood pressure.[25, 44]

The pressure volume index (PVI) is an assessment of this compliance such that $PVI = \Delta V/\log_{10}(P_P/P_0)$, where δV is the volume of the fluid bolus, P_P is the peak ICP after bolus injection, and P_0 is the baseline ICP. In normal adults about 25 mL is required to raise baseline ICP by a factor of 10, giving a PVI of 25 mL. Because PVI is proportional to neural axis volume, in infants, the normal PVI is 10 mL.[44]

Four *imaging modalities* that aid in the assessment of intracranial hypertension are skull films, ultrasonography, computed tomography (CT scan), and magnetic resonance imaging (MRI). Findings on skull films, in chronic intracranial hypertension, include (1) the "beaten copper sign" and (2) splitting of the sagittal sutures. (In infants and young children cranial sutures should not exceed 2 mm and should not have bridges or closures.)[22, 48] Ultrasonography of the brain is useful in the premature and term infants because it avoids exposure to radiation, is relatively inexpensive, does not require sedation, and may be performed at the bedside. The real-time sector scanner uses the anterior fontanelle as an acoustic window and can visualize almost all portions of the brain.[18] CT scan and MRI, both of which are discussed below, provide excellent images of the etiology of the intracranial pathology giving rise to intracranial hypertension.

Certain neurosurgical conditions are associated with disturbances in the cardiorespiratory centers of the brain stem. Disturbances in the respiratory center are common in infants with congenital abnormalities of the hindbrain. Sleep studies in infants with myelomeningocele show that they have longer periods of apnea and lower mean heart rates than normal infants. In addition, laryngeal dysfunction, stridor, and swallowing disorders may be present. Posthyperventilation apnea is common in infants and in the adult with forebrain disease. Respiratory arrhythmias (tachypnea, bradypnea, and apnea) may indicate compression of the brain stem. Respiratory arrhythmias may be episodic and recurrent and may represent a type of brain stem failure.[11, 12, 37]

Intracranial pathology may also disturb the function of the cardiovascular center. Transtentorial herniation is initially associated with an increase in vagal tone. Pontine lesions are associated with tachycardia. As discussed previously, intracranial hypertension is classically associated with Cushing's triad of hypertension, bradycardia, and tachypnea.[25, 37]

Neurogenic pulmonary edema is a clinical syndrome associated with acute hypoxia, pulmonary congestion, pink frothy protein rich pulmonary edema, and radiographic evidence of pulmonary infiltrates. It is associated with a variety of intracranial pathologies including intracranial hemorrhage, head trauma, and seizure disorders. Both ischemia of the medulla and distortion of the brain stem are believed to be important to the activation of sympathetic and vagal centers in the medulla that lead to alterations in hydrostatic factors, permeability factors, and lymphatic drainage resulting in neurogenic pulmonary edema.[2, 3, 10, 33]

Electrocardiographic (ECG) changes may be associated with intracranial pathology. The ECG of the head-injured patient may show large P waves and prolonged QT intervals. Subarachnoid hemorrhage may be accompanied with a long QT, PR interval, large U waves, peaked P waves, and ST- and T-wave changes.[2]

Disturbances in metabolism may also accompany intracranial pathology. Both hyperglycemia (cerebral diabetes) and hypoglycemia are seen. Water intoxication due to inappropriate antidiuretic hormone secretion may result in hyponatremia. Diabetes insipidus may result in hypernatremia. Disturbances in thermoregulation may produce hyperthermia and hypothermia.[4]

Disturbances in neurologic function arising from injury to the cervical cord may also affect function in both the vital respiratory and cardiovascular systems. Acute cervical cord injury results in an impairment in alveolar ventilation, the severity of which is predictable from the level of cord injury. Transection of the cord at the level of C4 severely impairs diaphragmatic and intercostal muscle function. Transection of the cord at C6 spares diaphragmatic muscle function but results in a loss of intercostal muscle function. Spinal cord edema or hemorrhage subsequent to the initial injury, which extends to involve the anterolateral portion of the cervical cord in the C2–C4 area, results in sleep apnea.[38]

Acute cervical cord injury results in an initial hypertensive response followed by systemic hypotension. In dogs, the initial massive sympathetic activity is associated with histologic evidence of myocardial damage. Subsequent unopposed parasympathetic nervous system activity may be associated with sinus arrythmia, atrial fibrillation, ventricular ectopy, and ECG evidence of ST- and T-wave changes.[19, 29, 41]

The preoperative assessment of the neurologic function in the neurosurgical patient with a chronic cervical injury should include a specific assessment of autonomic nervous system function. Orthostatic hypotension arises from a loss of compensatory cardiovascular reflexes. Autonomic hyperreflexia is understood to arise from visceral and somatic sensory input, via pudendal and pelvic afferents, into the injured spinal cord, which is isolated from inhibitory modulation by the higher centers. Spinal reflexes result in violent muscle spasms, intense autonomic output over splanchnic efferent, or a release of catecholamines from the adrenal gland. The intense sympathetic discharge results in diaphoresis, cutaneous anserina (goose flesh), pupillary dilation, and severe life-threatening hypertension that may lead to acute pulmonary edema and retinal, cerebral, and subarachnoid hemorrhage. Patients may exhibit vasoconstriction and pallor below the level of cervical cord transection, with vasodilation and flushing above the level of injury. Bradycardia mediated by baroreceptor afferent and vagal efferents may occur. In the preoperative assessment, a history of paroxysmal episodes of facial tingling, nasal congestion, headache, shortness of breath, nausea, and blurred vision may identify the patient at risk for autonomic hyperreflexia. The majority of quadriplegics with injuries above T6 will manifest signs and symptoms of autonomic hyperreflexia. About a third of paraplegics with midthoracic lesions (T8–T12) are at risk for autonomic reflexia.[29, 42]

Preoperative investigation of the neurosurgical patient with a disturbance in neurologic function includes (1) the patient with a focal motor and sensory neurologic deficit, (2) the patient with epilepsy, and (3) the patient with global neurologic dysfunction and coma.

The history and physical findings of the patient presenting with a change in *focal neurologic function* give important clues to the site and nature of the underlying lesion. For instance, the presentation of the child or young adult with a recurrent nonspecific history of gastrointestinal upset and headache, suboccipital headache, vomiting, clumsiness and associated with the physical findings of ataxia and papilloedema is suggestive of a tumor in the posterior fossa. A chronic history suggests a cerebellar astrocytoma.[17, 45] An acute history suggests a medulloblastoma.[14] An older child or adolescent presenting with visual complaints, headache, accompanied by the physical signs of see-saw nystagmus, papilloedema, and visual field deficits suggests a craniopharyngioma. Symptoms and signs of associated hypothalamic-pituitary axis dysfunction are present in about half of patients with craniopharyngioma and include shortness of stature, diabetes insipidus, obesity, hypothyroidism, and hypocorticolism.[23] The presence of a pineal tumor is suggested by the findings of retraction nystagmus, vertical gaze palsy, a dissociation of pupillary light response, precocious puberty, diabetes insipidus, and pituitary dysfunction.[5] The adult presenting with seizures, headache, and neurologic deficits including personality changes, hemiparesis, monoparesis, or sensory loss suggests a lesion in the supratentorium. An acute history suggests an intracranial hemorrhage. A chronic history suggests a tumor.[21, 25, 27, 31]

During the last two decades improvements in the imaging modalities, namely CT scan and MRI, have virtually replaced the older modalities of skull films, nuclear medicine, pneumoencephalography and now allow a precise anatomic localization of the intracranial lesion. It is beyond the scope of this review to discuss the specific radiographic features of the various intracranial masses that may give rise to neurosurgical pathologies. Interested readers are referred to standard neurosurgical and neuroradiologic textbooks on this subject. However, a brief overview of the use of CT scanning and MRI in the preoperative assessment of neurologic dysfunction is warranted.

Both CT scan and MRI use images composed of two-dimensional arrays of elements that, when assembled, portray a cross section of intracranial contents. The fundamental difference between the two techniques relates to the factors that determine the signal intensity. For CT scan, only one variable determines the intensity of the image, namely the attenuation or absorption of the incident x-ray beam, such that the greater the electron density of an area the brighter the signal. This results in excellent contrast between CSF-filled compartments and neural tissue, but a lesser distinction between gray and white matter, although enhancement with contrast mediums capable of crossing the damaged or defective blood–brain barrier may improve visualization.[26, 28]

The MRI has an advantage over CT scanning because it avoids the need for exposure to radiation but has the disadvantage of not being easily applied to the patient in need of life support. The MRI involves the disturbance of protons by radiofrequency pulse sequences and the measurement of the echo signal emitted by the disturbed protons.[1] The lower threshold of MRI compared with CT for detection of brain edema accounts for the major diagnostic advantage of MRI in neurodiagnosis. Unlike CT scan, the signal intensity in MRI is determined by more than one variable. The determinants of signal intensity include the tissue characteristics, the movement of protons, and the tissue-specific exponential relaxation time constants. Relaxation times vary over a wide range and are the main source of contrast images of the brain in MRI. The differences in tissue relaxation times can be manipulated by the radiofrequency of the pulse sequences and the repetition times. Tissue characteristics may be increased with MRI enhancement by using paramagnetic substances possessing one or more unpaired electrons, which alter proton density and therefore signal intensity.[26, 28]

In addition to showing the anatomic relationship of the lesion, diagnostic imaging techniques may suggest perioperative treatments. Basal midline tumors, not associated with hydrocephalus, may be amenable to lumbar drainage to facilitate intraoperative decompression of supratentorial lesions. Cerebral aqueduct stenosis with hydrocephalus above and below the level of obstruction may indicate the need for placement of supratentorial and infratentorial drains to allow simultaneous relief of intracranial hypertension above and below the level of obstruction.

Superconductors may, in future, assist in the preoperative assessment of neurosurgical patients. These superconductors have minimal resistance. When placed in a magnetic field even weak electrical fields, such as that produced by the brain, will induce a current.[50]

Important diseases of the cerebral vasculature manifesting as intracranial hemorrhage or vaso-occlusion may present clinically as intracranial hypertension or neurologic deficit. Selective carotid arteriography is used to evaluate cerebrovascular disease and vascular supply of intracranial lesions. The anesthetist may be involved with the anesthetic management of these patients during diagnostic procedures, particularly in children. Although hypocarbia may enhance the quality of the arteriogram, it should be used cautiously in cerebral vascular disease, including arteriosclerosis and moyamoya disease.[43]

Neurosurgical management of *epilepsy* includes partial frontal, temporal, or occipital lobectomy. Hemispherectomy may also be indicated. Subcortical surgery, including section of the corpus callosum and other subcortical pathways, may be indicated for epileptic foci not confined to cortical areas.

Patients who may benefit from surgical excision of epileptic foci include patients with (1) intractable seizures and a failure of medical management to control seizures, (2) a significant impairment of cognition, behavior, and socialization, and (3) documented evidence of the focal origin of the seizures. A description of the onset and progression of the seizure should support the diagnosis of focal epilepsy. Motor manifestations of epileptic foci are typically one of three presentations: (1) an initial tonic clonic movement in a localized area followed by a definite Jacksonian march, (2) an adversive motor attack with the head and eyes turned to the opposite side, and (3) an inhibitory motor phenomenon presenting as a weakness of an extremity. Somatic sensory beginnings of a fit are also common. Focal epilepsy arising from frontal lesions may begin with a sudden loss of consciousness. The conclusion of a convulsion may also give clues to the location of the epileptic foci because the discharging foci fire earlier and longer than the normal cortex.[32, 35, 46]

Four noninvasive modalities are used in the assessment of the patient with focal epilepsy: (1) diagnostic imaging techniques of MRI and CT scan, (2) electroencephalography, (3) positron emission tomography, and (4) single-photon emission CT. The presence of a structural lesion is suggestive of the site of origin of the focal seizures; however, the relationship between the structural abnormality and focal epileptogenic discharge should agree.

Electroencephalography is essential to the preoperative assessment of the patient with epilepsy. The electroencephalogram measures the electrical activity arising from the brain. As such it represents a summation of neuroelectric events occurring near the brain's surface. Placement of the surface electrodes is based on the 10 to 20 International System of Electrode Placement. In addition, special nasopharyngeal or sphenoidal electrodes may be used to clarify the nature of discharging foci in the medial aspect of the temporal lobe. Each channel records the electropotential difference between two electrodes. Normally voltages range from 10 to 200 μV. During overt seizure activity peak voltages may exceed 500 μV. Abnormal waveforms suggestive of epileptiform foci include sharp waves, spike waves, spike and waves at a frequency of 3 Hz, and slow wave complexes at frequencies of less than 2.5 Hz. Simple maneuvers such as hyperventilation and photic stimulation may elicit abnormal wave complexes. Development of electroencephalographic video monitoring capabilities allow documentation of electroencephalographic events at the onset of seizures. This type of preoperative assessment allows identification of seizures that are not of cerebral origin and the focal nature of seizures.[24]

Positron-emission tomography is a relatively new modality for assessment of cerebral function. It allows measurement of regional use of brain substrate with positron-emitting isotopes (^{11}C, ^{3}N, ^{15}O). Such a modality provides an assessment of the metabolic fate of oxygen, water, glucose, and carbon dioxide. Regional blood flow may be studied with neutral lipophilic γ-emitting agents ^{123}I and ^{99m}Tc. The SPECT scan uses ^{123}I amphetamine to assess regional blood flow.[9, 20]

The seizure focus must be in an area of "dispensable brain" where resection will not lead to an unacceptable neurologic deficit. Resection is ill-advised in the sensorimotor cortex and in areas necessary for speech and recent memory. Therefore, preoperative assessment of the epileptic patient for surgical excision of the epileptic focus must also involve selective carotid amobarbital injection to assess speech dominance and memory function.[35, 46]

In the preoperative assessment of the *patient with coma,* the history is often brief. Assessment is based primarily on the physical examination. The Glasgow Coma Scale (GCS), developed in 1977 considered the state of consciousness, the pattern of breathing, pupillary responses, eye movements, and motor responses in order to derive a total score. It has been simplified to record the best motor response, best verbal response, and best eye opening to derive a total score (Table 1).[6] As such it can be used to guide treatment to allow prompt early and aggressive control of ICP. A GCS less than 6.0 suggests acute intracranial hypertension. A study of arterial blood gases drawn within 20 minutes of isolated head injury in adults showed that a GCS score less than 10 was associated with a PaO_2 of less than 80 mm Hg and a $Paco_2$ of greater than 45 mm Hg. There was good correlation between the severity of the head injury (low GCS score) and the degree of hypercarbia such that $Pco_2 = 64.5 - 2.1(GCS)$.[36]

Cerebral death results from irreversible brain damage such that internal homeostasis cannot be maintained. Cerebral death is identified in the normothermic unparalyzed unsedated patient who has not received CNS depressant drugs by (1) coma—the absence of responsiveness and movement to stimulation indicating the loss of cerebral hemispheric function, and (2) a fixed heart rate, absent decorticate and stretch motor reflexes, unresponsive cadaveric pupils, absent oculovestibular (doll's eyes) and caloric responses, vasoparalytic dopamine-dependent shock, and apnea unresponsive to elevations in carbon dioxide tension, indicating a loss of brain stem function.[20, 37] The transcranial Doppler is useful to assess CBF. It is based on the Doppler principle of the change in sound frequency produced by a moving object. In transcranial Doppler, the red blood cell is the moving object. The fontanelle, the squamous temporal bone, and large neck vessels have all been used as Doppler windows.[4]

Table 1. SIMPLIFICATION OF THE GLASGOW COMA SCALE

Response	Score
Best motor response	
Obeys commands	6
Localizes pain	5
Withdraws from pain	4
Abnormal flexion	3
Abnormal extension	2
Flaccidity	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate	3
Incomprehensible	2
None	1
Eye opening	
Spontaneous eye opening	4
Opens eyes to voice	3
Opens eyes to pain	2
None	1

The majority of patients who present with a disturbance in *spinal cord function* require surgical correction of congenital anomalies of the spinal column or craniocervical junction or surgical decompression of an injured or ischemic spinal cord. Preoperative assessment of neurologic function of the patient presenting with spinal cord pathology is based on the identification of associated intracranial pathology, including an assessment of ICP, and the assessment of the integrity of the long tract and neural synapses within the spinal cord. As with the assessment of intracranial pathology, the cornerstone of preoperative assessment of spinal cord pathology rests with the history and physical examination.

Myelodysplasia is a congenital condition arising from the failure of closure of the neural tube during embryogenesis and includes, in physical expression, the conditions of anencephaly, encephalocele, myelomeningocele, and spina bifida. The majority of infants with myelomeningocele subsequently develop hydrocephalus in the neonatal period. Hydromyelia complicates more than half of patients with myelomeningocele. Progressive dilation of the central canal of the spinal cord is associated with a rapidly progressive scoliosis and upper and lower limb motor loss.[15, 34, 39]

Antenatal ultrasonography is now the usual method of diagnosing myelodysplasia. The diagnosis may be supported by increased α-fetoprotein levels in maternal blood. Further preoperative imaging techniques are rarely necessary before surgical closure of the neural tube defect.

Congenital anomalies of the *craniocervical junction* have as a common pathology an abnormal relationship of the bony structures that make up the foramen magnum. Myelography of the craniocervical junction is a useful diagnostic modality.[47]

Myelodysplasia is associated with the Arnold-Chiari malformation, which includes the anatomic findings of an elongation of the brain stem and fourth ventricle and displacement of the cerebellar vermis through the foramen magnum, resulting in hydrocephalus. Symptoms associated with the Arnold-Chiari malformation include pain at the skull base and neck, upper limb weakness, nystagmus, dysfunction of the lower cranial nerves, hypotonia, or spasticity. Myelodysplasia is also associated with the tethered cord syndrome.[15, 16, 34, 39]

Basilar impression is associated with the indentation of the skull base by the cervical spine, which decreases the volume of the posterior fossa. Less than half of cases are symptomatic, but symptoms include headache, motor weakness, paresthesias, and cranial nerve dysfunction. Drop attacks and amaurosis fugax may arise if vertebral basilar compression occurs. Physical examination often reveals a patient with a short stocky neck and some restriction in neck motion. Signs of neurologic dysfunction include nystagmus, paraparesis, hypoglossal nerve dysfunction, and ataxia.[16, 47]

Patients with conditions causing compression of the spinal cord present with pain and a disturbance in neurologic function. Localized pain to a specific area suggests extradural compression. Radicular pain suggests an intradural lesion. Diffuse distal pain or pain along the entire spinal axis suggests involvement of the spinal cord. Pain may be increased when the patient is recumbent due to venous engorgement of the epidural plexus. Intramedullary tumors of the spinal cord often present with a longstanding history and progressive disturbance in gait, clumsiness, and motor regression. Cervical cord involvement may be associated with a head tilt and torticollis. Thoracic cord involvement may be accompanied by a scoliosis. Disturbances in CSF flow may give rise to intracranial hypertension.[15]

Diagnostic imaging modalities include spine films, myelography, CT scanning, ultrasonography if a previous laminectomy was done, and MRI, which is the imaging technique of choice.[15]

In the last decade evoked potentials have been used to assess spinal cord conduction. Sensory-evoked potentials follow stimulation of peripheral nerves and may be useful in the preoperative assessment of intrinsic spinal cord disease, spinal cord compressive disorders, craniovertebral anomalies, and traumatic spinal cord injuries. The somatosensory-evoked response is a triphasic wave. The primary response after stimulation of the peripheral nerve is carried in the dorsal columns of the spinal cord. However, the anterolateral columns contribute to the secondary waveforms. Conduction velocity ranges from 50 to 60 m/s in the normothermic individual. If conduction velocities are prolonged and if the initial latency is delayed, then spinal cord pathology probably exists.[13]

Motor-evoked responses for assessment of the motor tracts are also being investigated. The cranial stimulating plate is placed over the motor cortex and palate and the recording electrode made between the spinous process in the cervical, thoracic, and lumbar areas. Motor tract conduction velocity exceeds 60 to 70 m/s.[13]

In 1930 Harvey Cushing wrote, "The morbid anatomy of the lesions is greatly obscured by the imperfections of our methods of examination, but still more because they are but rarely seen at the autopsy table and then only in their terminal stages."[7] State-of-the-art diagnostic imaging modalities now allow precise anatomic delineation of the brain and spinal axis before surgical intervention. Developments in the assessment of neurologic function will, in the future, allow a more precise correlation between disturbances in neurologic structure and function.

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DO EVOKED POTENTIALS HAVE ANY VALUE IN ANESTHESIA?

Arthur M. Lam, MD, FRCPC

The generation of cerebral electrical potentials in response to stimulation of peripheral nerves (sensory-evoked responses or potentials) was first observed by Caton in 1875,[13] but it was not until 1974 before Dawson introduced it into clinical practice as a diagnostic tool.[19] Although its use has gained wide acceptance in many centers,[44, 45, 48] there continues to be a debate about the merits of intraoperative monitoring of evoked potentials.[5, 18, 31, 96] This article briefly reviews the physiologic basis of evoked potential (EP) and evaluates the value of intraoperative monitoring of EP in anesthetized patients. For the purpose of this review, EP will include both sensory-evoked potential (SEP) and motor-evoked potential (MEP). The latter includes monitoring of cranial nerve function as well as the motor potentials generated in response to transcranial electrical or magnetic stimulation. The discussion on transcranial MEP is brief because this technique remains largely experimental.

ELECTROPHYSIOLOGIC BASIS OF SENSORY-EVOKED POTENTIAL

The SEPs are electrical potentials generated in response to stimulation of a peripheral nerve or cranial nerve. The stimulus can be acoustic, electrical, or mechanical. These potentials are thought to arise from (1) action potentials or (2) graded postsynaptic potentials during the propagation of the electrical impulse from the periphery to the brain and can be recorded over the scalp as well as at various sites along the anatomic pathway using surface electrodes.[41] Thus, SEPs are pathway specific, stimulus specific and event related and are

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different from the electroencephalogram (EEG), which is random in nature.[16] The amplitude of SEP is small compared with EEG, therefore necessitating the use of computer averaging or summation to extract the SEP signals from the background EEG noise.

CLASSIFICATION AND COMMON MODALITIES OF SENSORY-EVOKED POTENTIAL

Similar to electrocardiographic signals, SEPs are volume-conducted and can be recorded from scalp electrodes in response to stimulation of any peripheral nerve or cranial nerve, although the largest amplitude is recorded over an area where the electrical dipole generated in response to the stimulus is maximal. SEPs can be near-field (the neurogenerator sited near the recording electrode, e.g., cortical EP) or far-field (e.g., brain stem EP). As the far-field EPs occur early they are also referred to as short-latency EPs. The late cortical components are referred to as intermediate or long-latency potentials.[44, 48] For any given sensory anatomic pathway, by selecting the appropriate time base, one can record either the brain stem or cortical component or both. The brain stem components are usually generated within 10 ms of the stimulus and the early cortical components generated within 50 to 100 ms, depending on the site of stimulation. Later cortical components represent cognitive functions, tend to be more susceptible to anesthetic influence, and are therefore seldom used for intraoperative monitoring, although they may be useful for monitoring depth of anesthesia (see following discussion). The three most commonly used modes of SEP are (1) brain stem auditory-evoked potential (BAEP), (2) somatosensory-evoked potential (SSEP), and (3) visual-evoked potential (VEP). The representative tracings are shown in Figure 1. Although BAEP is by definition a brain stem EP and SSEP monitoring generally refers to the cortical component, both modalities have brain stem as well as cortical and late cortical components. VEP, on the other hand, is exclusively a cortical EP. Spinal EPs can also be recorded from surface electrodes placed over the spinal column.

All three modalities have found widespread clinical applications in the neurologic assessment of patients with equivocal symptoms or in patients who cannot be reliably assessed due to lack of cooperation or inability to communicate. This review restricts the discussion to the use in patients who cannot be assessed clinically due to the state of general anesthesia.

The SSEPs are commonly recorded over the parietal cortex in response to electrical stimulation of the contralateral median nerve or posterior tibial nerve (Fig. 1). Other peripheral nerves including the ulnar nerve, common peroneal nerve, and femoral nerve can also be used. Spinal cord potentials are recorded over the cervical spine (usually C2 or C7) or lumbar spine. Recording these spinal potentials provides confirmation of stimulation of the posterior columns should the cortical response become attenuated. By using a noncephalic reference, somatosensory brain stem EP can also be recorded. BAEP is recorded over the vertex in response to monaural or binaural stimulation of the auditory nerve, generally using sound clicks delivered with headphones or ear-insert transducers. VEP is recorded over the occiput in response to visual stimulation. In the awake patient this takes the form of checkerboard pattern reversal presented on a video monitor, and in the anesthetized patient, flashing lights through closed eyelids, using light-emitted diode goggles, are used instead. A large part of the intraoperative variability of VEP is due to the lack of a suitable stimulus for the anesthetized patient. Because of this variability and unreliabil-

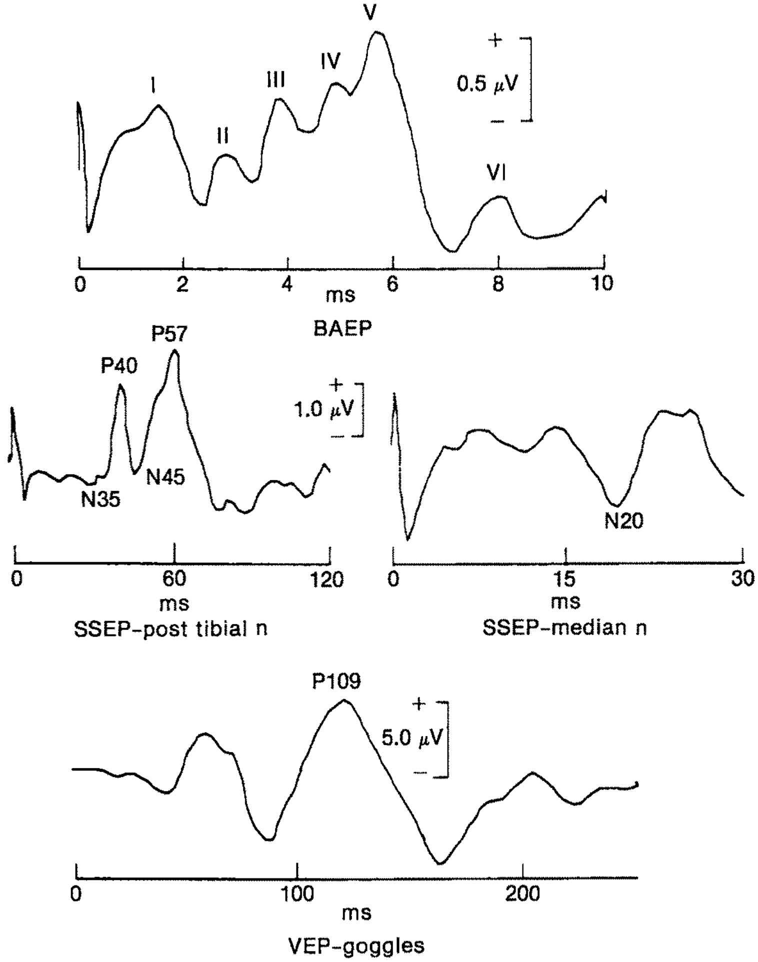

Figure 1. Common modalities of sensory-evoked potentials. BAEP = brain stem auditory potential; SSEP-median n = somatosensory-evoked potential with median nerve stimulation; SSEP-post tibial n = somatosensory-evoked potential with posterior tibial nerve stimulation; VEP-goggles = visual-evoked potential in response to stimulation with light-emitted diode goggles (*From* Lam AM: Monitoring neurologic evoked responses. The American Society of Anthesiology Refresher Course 17:175, 1989; with permission.)

ity, intraoperative VEP monitoring has little or no application[14, 118] and is not discussed further.

ELECTROPHYSIOLOGIC BASIS OF MOTOR-EVOKED POTENTIAL

Transcranial Electrical or Magnetic Stimulation of Motor Cortex

Stimulation of the motor cortex with an electric current resulting in impulse propagation in the motor tracts was first described by Merton and Morton.[95]

The electrical stimulation directly excites the axons, generating an early wave (D wave) and indirectly a later component (I wave), which results from repetitive synaptic activation of pyramidal tract neurons.[156] These waves can be recorded over the medullary pyramid or contralateral corticospinal tracts. In response to these waves, nerve action and muscle action potential can be recorded over the extremities.[75, 76] The electromyographic responses (EMG) recorded are often simply referred to as MEPs. Electrical stimulation, however, is painful in the awake subject. Subsequently Barker et al[6] demonstrated that a motor response can also be evoked with transcranial magnetic stimulation, which does not cause pain or discomfort. These motor responses can be assessed by visual inspection of limb movements or recording of EMG (MEP) in the tibial or thenar muscles. The magnetic stimulation is also effective when applied to the motor tracts, e.g., over the brachial plexus. Optimal monitoring of MEP necessitates the omission of neuromuscular blockade or at least a partial maintenance of neuromuscular function as part of the anesthetic management. The magnitude of MEP is many times that of SEP; therefore, little or no computer averaging is required. As SEP only monitors the sensory pathway function, MEP monitoring complements SEP monitoring. Considerable investigations have been done, attesting to the potential utility of this monitoring technique.[74, 76 159] Further developments, however, are hampered by the fact that MEPs are severely attenuated by anesthesia (see following discussion). Limited clinical investigations using the criterion of 50% reduction in amplitude as significant change (similar to SSEP monitoring) suggest that MEP monitoring may lack specificity.[159] Until more definitive studies are done, intraoperative MEP monitoring remains an investigative tool only.

Intracranial Electrical Stimulation of Cranial Nerves

Intracranial electrical stimulation of any cranial nerve with motor fibers will result in recordable EMG in muscles supplied by their respective cranial nerves. Such monitoring helps to identify and preserve the functions of these nerves during posterior fossa procedures. Theoretically, cranial nerves III, IV, V, VI, VII, IX, XI, and XII can all be monitored. In practice EMGs are usually recorded from the masseter (V), orbicularis oculi (VII), orbicularis oris (VII), trapezius (XI), and the tongue (XII) using needle electrodes. In contrast to transcranial MEP, monitoring of evoked EMG of cranial nerves placed at risk is a well-accepted procedure.

EQUIPMENT REQUIRED FOR THE ACQUISITION OF SENSORY-EVOKED POTENTIAL

Data processing of the EEG to allow display of the SEP signals necessitates the following steps: acquisition of the electrical signals with appropriate filters, amplification, analog-to-digital conversion, signal averaging, and finally digital-to-analog conversion for the final display of the waveforms. Simple turnkey equipment are currently available from many commercial vendors. Detailed description of equipment and recording parameters are beyond the scope of this review and guidelines are available from the American Electroencephalographic Society[4] or a standard textbook.[106]

INTERPRETATION OF SENSORY-EVOKED POTENTIAL

The BAEP is characterized by a series of positive peaks conventionally labeled with Roman numerals. The purported neurogenerators for these peaks are I, auditory nerve; II, cochlear nucleus; III, superior olive; IV, lateral lemniscus; V, inferior colliculus; and VI, medial geniculate.[16, 44] For simplification, peaks II and III can be considered pontine in origin, whereas VI and V represent the midbrain (Fig. 1).

The SSEPs are also characterized by specific peaks and troughs that are labeled according to the polarity (positive or negative are often referred to as P or N) and the time at which they occur following the stimuli (latency). For example, N20 in SSEP-median nerve refers to a negative peak (or more correctly trough) that typically occurs 20 ms following the stimulus and signals the activation of the sensory cortex. Because the latency varies among individuals, some authors prefer to label them by the order of the occurrence rather than by latency. For example, P1 is the first positive peak, and N1 the first negative trough. (Some investigators prefer to plot positive peaks down and negative troughs upward.) For SSEP-median nerve, a derived latency parameter, the central conduction time (CCT), is frequently calculated from the latency difference between the potential recorded over the cervical spine and the cortex. This represents the time required for the impulse to travel from the brain stem to the cortex, and increase in the CCT is thought to be a sensitive index of ischemia.[54] In the diagnostic laboratory, individual patient response is compared with established normal reference population. For intraoperative monitoring, the patient acts as his or her own control and deviations from baseline recordings are interpreted within the context of surgical manipulation as well as consideration of other physiologic variables (see following). The significance of any change in the recordings is determined by the magnitude of decrease in amplitude or increase in latency. Ischemia or injury to the underlying neurologic structures generally results in a decrease in amplitude and an increase in latency or total abolition of the waveforms. Correlation of size of cerebral infarction with loss of SSEP has been established in a feline middle cerebral artery occlusion model.[142] However, no strict criteria for interpretation of these changes currently exist. With BAEP latency changes (wave V) appear to be more important than amplitude changes and an increase in latency (wave V) greater than 1 ms is generally considered to be abnormal. Whereas with SSEP the amplitude appears to be more important and the criterion that is generally accepted as a significant change is a reduction in amplitude by 50%.[106, 155] Recently a similar criterion of 50% amplitude reduction for wave V has also been proposed for BAEP monitoring.[129] An increase in CCT greater than 1.2 ms or an absolute value of CCT greater than 10 ms is also interpreted to be abnormal. With SSEP monitoring a change in amplitude frequently precedes a change in latency, perhaps because delays in conduction indicate more extensive injury or involvement of subcortical structures.[30, 59] Abolition of SEPs, however, does not necessarily imply permanent injury because prolonged disappearance with subsequent recovery has been observed to be compatible with normal neurologic function.

IMPORTANT VARIABLES IN INTRAOPERATIVE RECORDING OF SENSORY-EVOKED POTENTIAL

The operating room is a hostile environment electrically and minor current leakage from surrounding equipment or the continuous use of electrocautery may make it impossible to acquire adequate signals. To record SEPs reliably and consistently, it is important to ensure proper insulation of cables and placement of electrodes, including backups. Other confounding variables that may influence SEP include anesthetic agents (see following), change in body temperature, and fluctuation of arterial carbon dioxide tension (P_{CO_2}) and systemic blood pressure. Changes in P_{CO_2} and blood pressure within the physiologic range have no clinically significant effect on SEP,[22, 131] but this is not so with a change in body temperature. Although mild hypothermia is compatible with normal recordings,[68] a decrease in temperature below 34.5°C causes a progressive decline in amplitude and an increase in latency[67]; neither SSEP nor BAEP can be reliably recorded below 18°C.[17, 56] The development of hypothermia does not necessarily diminish the value of SSEP monitoring because unilateral injury to the pathway at risk can be inferred from differences between bilateral recordings, but does limit its usefulness as a monitor of global cerebral function during profound hypothermic cardiopulmonary bypass.

APPLICATION OF INTRAOPERATIVE MONITORING OF SENSORY-EVOKED POTENTIAL

There are two potential clinical applications for intraoperative monitoring of SEP: (1) SEP as an objective, physiologic assessment of the depth of anesthesia, and (2) SEP as an early warning signal to prevent or minimize impending neurologic injury. In conjunction with its potential use as a measure of depth of anesthesia, the influence of anesthetic agents on SEP and MEP will be summarized along with a recommendation of an anesthetic regimen suitable for intraoperative EP monitoring.

Depth of Anesthesia

Because SEPs are influenced by anesthetic agents in a predictable fashion, it has been suggested as a physiologic measure of depth of anesthesia.[135] An objective and useful indicator of depth of anesthesia must take into consideration the anesthetic dose as well as the impact of surgical stimulation, yet initial clinical experience and studies only assessed the dose-related changes in SEP with anesthesia. Recently, Sebel et al[137] reported that the amplitude of cortical SSEP increases with tracheal intubation and surgical stimulation. Other investigators have examined the use of late auditory evoked potentials (cortical) for this purpose.[87, 144, 148] Surgical stimulation was found to increase the amplitude of the long-latency auditory EP, albeit not consistently in all subjects studied.[148] The pursuit of these long latency cortical potentials for the purpose of monitoring depth of anesthesia represents a reasonable approach, but more definitive studies are required before optimism can be expressed. More recent studies examined the auditory steady state response[113, 114] (a sinusoidal waveform created by overlapping electrical potentials generated in response to fast sensory stimulation, usually at 40 Hz) as well as the contingent negative variation[29] (a late cortical potential whose generation is dependent on the subject's attention). These pursuits are somewhat reminiscent of earlier investigations with EEG as a determinant of anesthetic depth. At the present moment establishment of an objective and reliable electrophysiologic determinant of anesthetic depth remains an elusive goal.

In contrast, the influence of anesthetic agents on SEPs has been studied extensively, and these studies are necessary not only to allow the design of an anesthetic regimen suitable for intraoperative monitoring, but also to enable intelligent interpretation of intraoperative SEP changes. Influence of anesthesia on MEP has also been investigated.

Influence of Anesthesia on Sensory-Evoked Potential

The influence of anesthetic agents on sensory EP are not uniform, but several general statements can be made: (1) Intravenous agents have mild or limited depressive effects on all modalities of SEP (except etomidate and ketamine, which augment SEP; see following), whereas all inhalation agents cause a dose-related decrease in amplitude and increase in latency.* (2) The short-latency potentials such as BAEP are relatively resistant to anesthetic influence and can be recorded even during deep inhalation anesthesia, albeit with some increase in latency, while the intermediate and long-latency potentials are more susceptible and can be abolished by highdose inhaled anesthetics.[10, 15, 23–25, 27, 83, 89, 91, 92, 108, 109, 111, 123–126, 128, 133, 136, 145, 146, 147, 149, 153] (3) Subcortical and spinal EPs are relatively resistant to anesthetic influences.[82, 109, 153] The commonly used intravenous agents, including barbiturates and narcotics, cause statistically significant but clinically insignificant changes on BAEP, and although causing significant increases in latency and decreases in amplitude with SSEP, are compatible with satisfactory recordings even in high doses. Etomidate and ketamine, on the other hand, increase the amplitude of SSEP.[93, 132, 141] Although the mechanism remains unclear, this augmentation effect has been used to allow SSEP monitoring in patients with abnormally low and otherwise unrecordable signals.[141] With inhalation anesthetics, all three commonly used agents, isoflurane, enflurane, and halothane, cause an increase in latency with no apparent effect on amplitude with BAEP. This increase in latency, however, is small and, at least with isoflurane, exhibits a ceiling effect with no further increase beyond an end-tidal concentration of 1% (Fig. 2). With SSEP, all three inhaled anesthetics cause a dose-related increase in latency and decrease in amplitude, completely abolishing the cortical potential at high doses. Subcortical potentials (brain stem and spinal cord), however, appear to be more robust and can frequently be recorded even at doses high enough to abolish the cortical potentials. In addition, spinal cord–evoked potential recorded near-field using epidural electrodes are resistant to the influence of anesthesia, but, unlike scalp electrodes, obviously can only be placed intraoperatively. There is no consensus on the best inhaled agent for SSEP monitoring, with halothane suggested for median nerve stimulation in one study[111] and isoflurane suggested for posterior tibial nerve stimulation in another.[108] The illustrative changes from these two studies are displayed in Figures 3 and 4. There is no obvious explanation for the discrepancy, but what is clear is that low-dose inhaled agents (< 1 minimum alveolar concentration [MAC]) are compatible with intraoperative SSEP monitoring, particularly if nitrous oxide is omitted. Although nitrous oxide has no effect on BAEP (Fig. 5),[89, 134] it causes more than a 50% amplitude reduction in cortical potential in SSEP monitoring when added to a narcotic-based anesthetic.[92, 134, 140] This depressive effect of nitrous oxide appears to be magnified when added to an inhaled anesthetic.[10, 92, 108, 111] At equipotent doses, the depressive effect of nitrous oxide appear to exceed that

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*References 7, 10, 15, 23–25, 27, 63, 65, 80, 83, 89, 91–93, 108–111, 123–128, 130, 132–134, 136, 138–141, 145–147, 149, 153

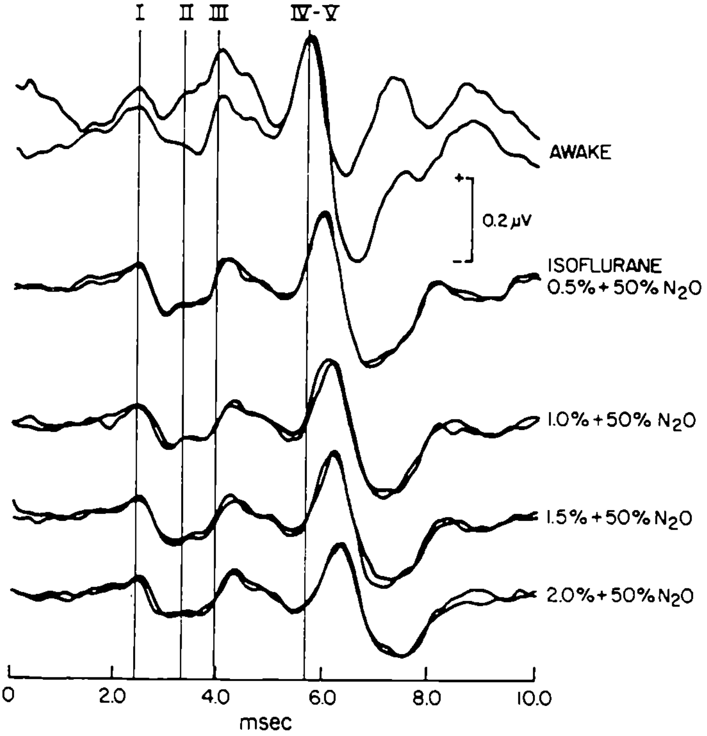

Figure 2. Influence of isoflurane and isoflurane-nitrous oxide anesthesia on BAEP. A ceiling effect was demonstrated with no significant increase in latency beyond an end-tidal concentration of 1.0% isoflurane. Nitrous oxide had no discernible effect compared with recording made during administration of isoflurane alone (tracings not shown). (*From* Lam AM: Monitoring neurologic evoked responses. The American Society of Anthesiology Refresher Course 17:175, 1989; with permission.)

of isoflurane (unpublished observation). Lidocaine, an often-used adjunct in neuroanesthesia, has negligible influence on BAEP and SSEP even when given as a continuous intravenous infusion to maintain serum levels between 3 and 4 μg/mL.[86, 122]

Influence of Anesthesia on Motor-Evoked Potential

Despite the fact that the magnitude of MEPs are several times that of SEPs and therefore require little or no averaging for recordings, intraoperative monitoring of MEP proves to be an extremely difficult task because of its exquisite sensitivity to anesthetic influence.[11, 28, 34–38, 46, 47, 157, 158] Most studies have been performed on primates[34–38] although some have been done in humans.[11, 157, 158] Electrical MEPs appear to be slightly more resistant to anesthetic influence than magnetic MEPs. Both are consistently abolished by inhaled agents even at low doses[11, 158] and not infrequently abolished by intravenous agents. Unlike their augmentative influence on SSEP, etomidate and ketamine reduce MEP amplitude, although they do appear to be the least depressant and their use is compatible with significantly reduced but recordable signals. In addition,

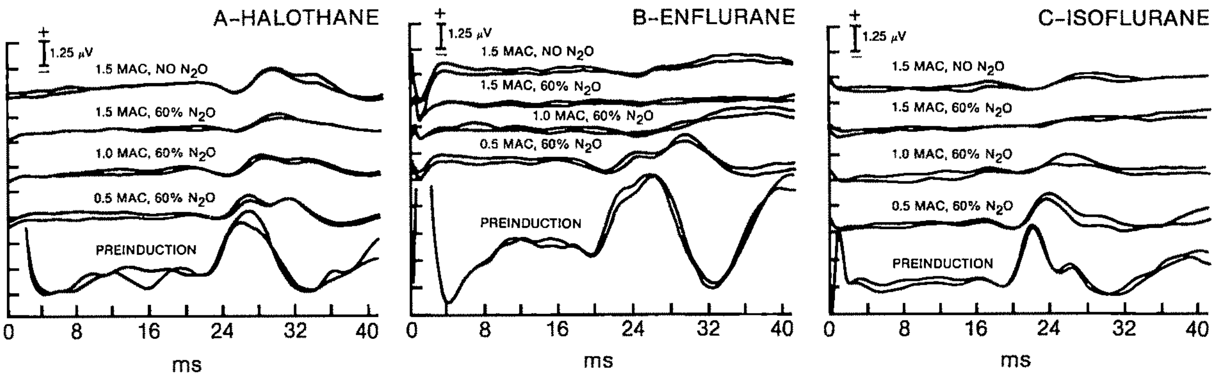

Figure 3. Representative SSEP cortical responses (C-3′ or C4′-FPz) (median nerve stimulation) recorded at various MAC levels of halothane (A), enflurane (B), and isoflurane (C) with 60% N_2O, and at 1.5 MAC without N_2O. (*From* Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 65:35, 1986; with permission.)

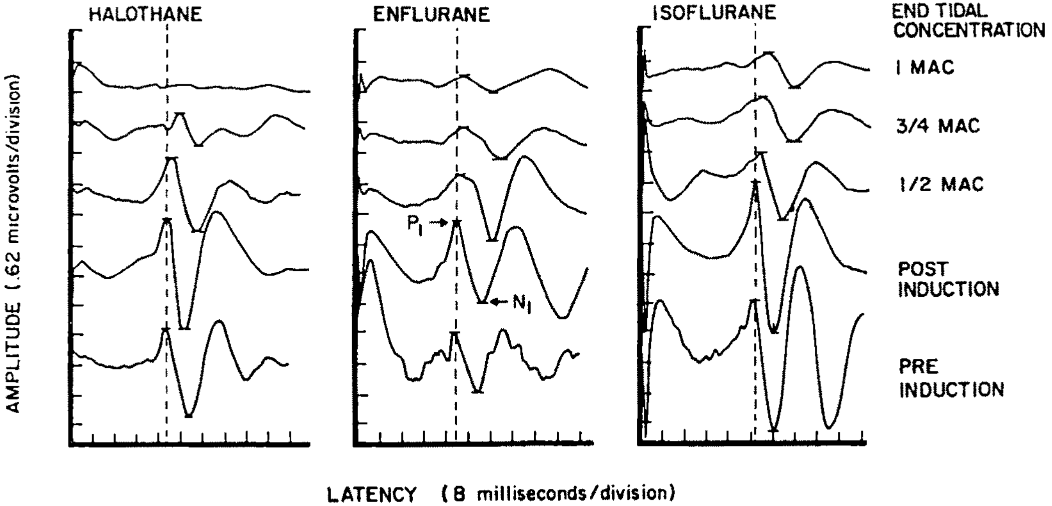

Figure 4. Intraoperative SSEP records (posterior tibial nerve stimulation) from three patients, each one receiving one of the volatile anesthetic agents plus 60% nitrous oxide. Peak latencies P_1,N_1 in msec; peak-to-peak P_1-N_1 amplitudes in microvolts. Postinduction SSEP serves as control. Note the increase in latencies and decrease in amplitudes with the increase of the MAC values of all three volatile anesthetics. Also note that, at 1.0 MAC of halothane, the SSEP is not measurable. (*From* Pathak KS, Amaddio M, Kalamchi A, et al: Effects of halothane, enflurane, and isoflurane on somatosensory evoked potentials during nitrous oxide anaesthesia. Anesthesiology 66:753, 1987; with permission.)

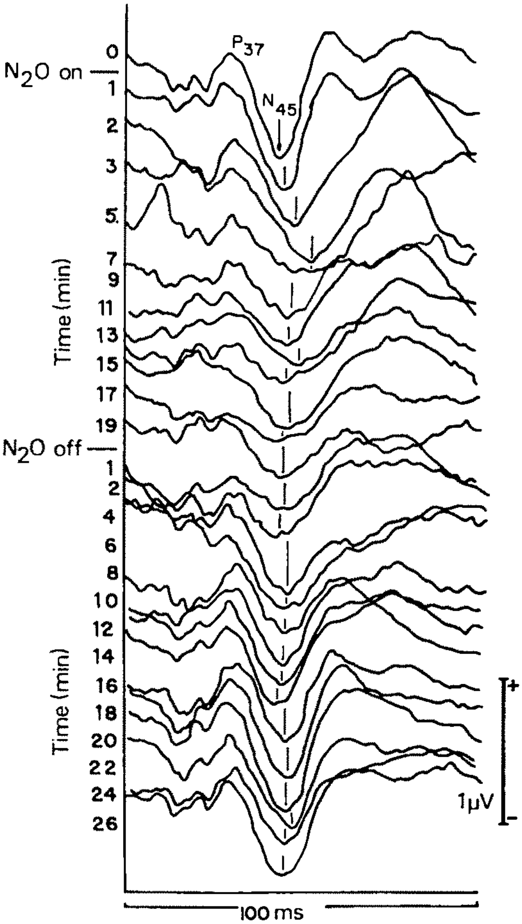

Figure 5. Serial cortical recordings of posterior tibial nerve somatosensory-evoked potentials during the introduction and withdrawal of nitrous oxide during closure after spinal cord tumor biopsy. The waves are plotted so that a relative positivity at vertex (C_z') is plotted upward. The peak of interest for this study at about 45 ms is indicated (N_{45}). (*From* Sloan TB, Koht A: Depression of cortical somatosensory evoked potentials by nitrous oxide. Br J Anaesth 57:849, 1985; with permission.)

complete neuromuscular blockade abolishes all MEPs recorded from the extremities. However, electrical MEPs recorded from the extradural space are resistant to general anesthesia, including the use of muscle relaxants.[60, 81]

With the exception of muscle relaxants, evoked EMG from cranial nerves are not susceptible to anesthetic influence and can be recorded with all anesthetic techniques. The influence of anesthetic agents on BAEP, SSEP, and MEP are summarized in Table 1.

Recommended Anesthetic Regimen

Brain Stem Auditory-Evoked Potential

Because of its robust nature, BAEP can be successfully monitored regardless of the anesthetic agent used. Intravenous agents have the least effect while

Table 1. INFLUENCE OF ANESTHETIC AGENTS ON SEP AND MEP

	BAEP			SSEP			MEP		
	Latency	Amplitude	Reference	Latency	Amplitude	Reference	Latency	Amplitude	Reference
Intravenous Agents									
Thiopental									
Low dose	↔	↔	27	↑	↔/↓	93, 139	↑	↓	158
High dose	↑	↓	24	↑	⬇	24			
Propofol	↑	↔	15, 126, 149	↑	↔/↓	91, 127	⬆	⬇⬇	*
Diazepam	↔	↔	83	↔	↔	83	?	?	
Midazolam	?	?		↔	↓	65, 138	⬆	⬇	35†
Etomidate	↔	↔	147	↑	⬆	65, 93, 141	⬆	⬇	36†
Ketamine	?/↔	?/↔	7‡	↔	⬆	61	⬆	⬇	34†
Fentanyl	↔	↔	83, 124	↑	↓	83, 93, 110 130	⬆	⬇	11, 28,† 37†, 158†
Sufentanil	↔	↔	*	↔	↓	63	?	?	
Alfentanil	?	?		?	?		?	?	
Lidocaine	↔	↔	86, 122	↔	↔	86	?	?	
Inhaled Agents									
Halothane	↑	↔	27, 146	⬆	⬇	92, 108, 109, 111, 123, 133	⬆	⬇⬇	47‡
Enflurane	↑	↔	25, 145 146	⬆	⬇	92, 108, 109, 111, 113	⬆	⬇⬇	47‡
Isoflurane	↑	↔	80, 89, 128 136	⬆	⬇	10, 92, 108, 109, 111, 125, 136, 153	⬆	⬇⬇	46‡, 47,‡ 11
Nitrous oxide	↔	↔	89, 134	↔	⬇	10, 92, 108, 109, 111, 134, 140	⬆	⬇	38†, 47‡, 157, 158

Symbols: ↔ = no influence; ↑ and ↓ = clinically insignificant changes; ⬆ and ⬇ = clinically significant changes; ⬇⬇ = may be abolished.
All references are based on human studies unless otherwise specified.
*Unpublished observation.
†Primate studies.
‡Rat studies.

inhaled agents cause a clinically insignificant increase in latency. Nitrous oxide has no discernible effect.

Somatosensory-Evoked Potential

This is best recorded during a narcotic low-dose isoflurane relaxant anesthetic. Alternatively a narcotic nitrous oxide relaxant anesthetic can be used. The combination of nitrous oxide and inhaled anesthetic is best avoided. Etomidate may be used to augment the amplitude in patients with abnormal responses, but once administered, must be maintained as an infusion.

Motor-Evoked Potential

Although this remains an experimental technique, and intraoperative recordings remain difficult, narcotic nitrous oxide ± etomidate infusion appears to be the best technique currently available for the recording of magnetic MEP. Muscle relaxants should be either avoided or given only to effect a partial blockade. No anesthetic restrictions apply to the monitoring of cranial nerve EMG except muscle relaxants.

Combined Somatosensory- and Motor-Evoked Potential (Cranial Nerve) Monitoring

The need for such monitoring is increasing and represents an anesthetic challenge. The author prefers to use a combination of low-dose isoflurane, fentanyl or sufentanil infusion plus a lidocaine infusion. Muscle relaxants and nitrous oxide are both avoided.

Regardless of the anesthetic regimen employed, a useful guideline is to maintain as near steady-state anesthesia as possible during recording of intraoperative SEP and limit changes in other physiologic variables such as temperature.

PREVENTION OF NEUROLOGIC INJURY

Intraoperative monitoring of EPs is most valuable when (1) a neural pathway amenable to monitoring is placed at risk during a neurosurgical procedure, (2) recording and stimulating sites are available and do not interfere with the procedure, and (3) interventional therapy can be implemented if significant changes are found. The surgical procedures where monitoring of EPs have been advocated are summarized in the following sections in order of usefulness.

Corrective Procedure on the Spinal Column

This is perhaps the procedure where intraoperative monitoring of SSEP has gained the widest and most ready acceptance,[9, 21, 40, 42, 73, 85, 97, 119, 151, 152] even though critics remain.[5, 18] Scoliosis surgery or Harrington instrumentation and similar surgical procedures on the spinal column are associated with only a low risk of neurologic injury of less than 1%, but the resulting disability is so devastating that it necessitates some means of detection before permanent injury occurs. By monitoring simultaneously the cortical and spinal potentials (above and below the surgical sites, respectively) generated in response to stimulation of the posterior tibial nerve or the common peroneal nerve, potential injury to the spinal cord may be detected during detraction. In addition to cortical monitoring with scalp electrodes, improved results can be obtained with the use of intradural and epidiural electrodes, the recordings from which are less susceptible to the influence of inhaled anesthetic agents. The different electrode sites used for such monitoring are shown in Figure 6. The use of SSEP monitoring obviates the need for the wake-up test, which is at best unpleasant for the patient and at worst dangerous. Although false-negative results have been reported[40, 73, 97] and the lack of changes in SSEP can be attributed to the different anatomic location of the sensory and motor tracts in the spinal cord,[160, 161] in each of these reported cases[73] there was an alternative plausible explanation.[31] These reports also serve to emphasize the importance of the following: (1) The anatomic pathway chosen for monitoring must be consistent with the portion of spinal cord at risk; median nerve SSEP will not detect spinal cord ischemia at the thoracolumbar level. (2) Simultaneous bilateral stimulation may strengthen the signals recorded, but it may also mask unilateral damage that may have been detected with alternating unilateral stimulation. (3) Intraoperative preservation of SSEP does not preclude the occurrence of postoperative neurologic deficits as ischemia and injury may develop in the immediate postoperative period. It is hoped that ongoing MEP research will eventually allow simultaneous monitoring of SSEP and MEP, with further improvement in patient safety.

Acoustic Neuroma and Other Cerebellopontine-Angle Tumors

Intraoperative monitoring of BAEP may help to preserve the eighth cranial nerve during this surgical procedure and is considered to be a routine monitor

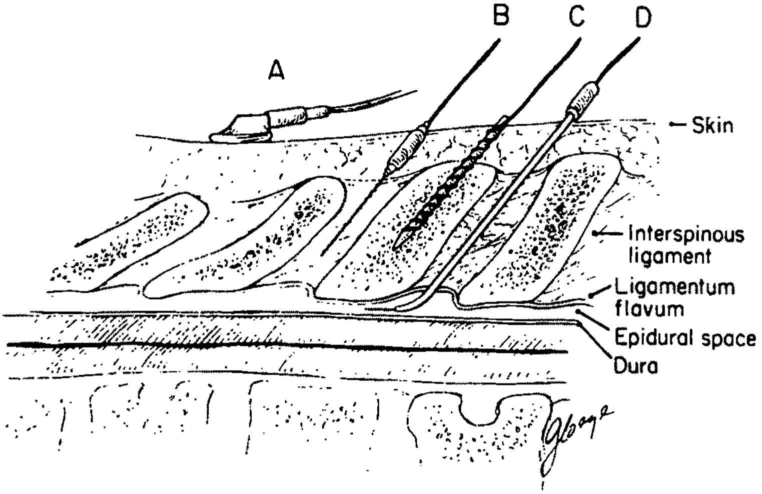

Figure 6. Comparison of four general types of electrodes used for recording spinal EPs. *A,* Disk surface electrode. *B,* Interspinous ligament electrode. *C,* Electrode screwed into the spinous process itself. *D,* Epidural electrode and the needle used for its placement. (*From* Nuwer MR: Evoked potential monitoring in the operating room. New York, Raven Press, 1986; with permission.)

in many centers.[1, 43, 49, 77, 99, 105, 107, 117] False-negative results seldom occur; if all components of BAEP disappear intraoperatively and fail to return, unilateral deafness usually results. Change in wave V amplitude or latency alone, however, is a poor prognosticator of postoperative hearing functions. The predictability and therefore the chance to preserve hearing can be increased by simultaneous monitoring of the electrocholeogram or direct intracranial recording of the auditory nerve.[77, 99] False-positive results do occur because brain stem retraction may cause transient loss of the waveforms. In addition, patients with large acoustic neuroma frequently have very abnormal or absent BAEP to begin with and therefore monitoring may not be possible. In one reported series only 33% of patients were amenable to intraoperative BAEP monitoring.[105] The value of this monitoring, however, is well established in patients with small tumors and preserved hearing preoperatively.[77, 105, 107]

Posterior Fossa Microvascular Decompression

Both cranial nerves VII and VIII are potentially at risk of damage during these procedures. Intraoperative monitoring of BAEP and seventh-nerve EMG help to identify these structures and preserve their functions. Significant reduction in morbidity attributed to such monitoring techniques has been reported.[32, 116]

Neurovascular Procedures

Cerebral Aneurysm Clipping

Monitoring of SSEP, particularly the CCT, has been found to be useful and to correlate with neurologic outcome in some patients.[12, 33, 62, 88, 102, 103, 143] BAEP monitoring, on the other hand, may be valuable in vascular procedures in the posterior fossa where the brain stem is potentially at risk.[52, 57, 69, 71, 78, 79, 112] With the recent trend toward using temporary occlusion of major feeding vessel instead of systemic hypotension to facilitate aneurysm clipping, EP monitoring may well become essential in cerebral aneurysm surgery. However, neither modality is very specific, and although good correlation with postoperative neurologic outcome can be demonstrated, both false-negative and false-positive results occur. Recent reports on the use of SSEP monitoring during temporary clipping and the associated false rates are summarized in Table 2. The relatively high false-positive rates are not unexpected, because the nature of electrophysiologic monitoring dictates the potential existence of an ischemic state where blood flow is inadequate for electrical function but enough to sustain viability

Table 2. SSEP MONITORING DURING TEMPORARY ARTERIAL OCCLUSION FOR CEREBRAL ANEURYSM SURGERY

Authors/Reference	Year	No. of Patients	Temporary Occlusion	False-Positive (%)	False-Negative (%)
Manninen et al[88]	1990	157	97	43	14
Mooij et al[103]	1987	5	5	?	0
Momma et al[102]	1987	40	40	60	5
Kidooka et al[62]	1987	31	15	38	22
Symon et al[143]	1984	34	15	40	7

should normal blood flow be restored in time (the ischemic penumbra). A certain false-positive rate thus appears to be unavoidable. In addition, false-negative results can occur. Because the monitoring is pathway specific, discrete injury not involving the anatomic pathway cannot be detected. In posterior circulation aneurysm surgery the simultaneous recording of both SSEP and BAEP may improve the results and more clinical studies are needed before the routine use of such monitors can be advocated.

Carotid Endarterectomy

The utility of SSEP monitoring in this procedure to determine the need for shunting during cross-clamp of the carotid artery has been reported in several series.[3, 8, 20, 39, 55, 70, 72, 90, 104, 120, 121, 150, 154] Because SSEP monitors the functional integrity of the entire anatomic pathway, it may be able to detect both cortical and subcortical ischemia, a distinct advantage over conventional EEG. On the other hand, it is unable to detect cortical ischemia other than the somatosensory cortex. There is no agreement on what components of the cortical potential should be used for monitoring; both early and late cortical potential have been used, and in one study a correlation between long-latency EP changes during cross-clamping and postoperative psychological dysfunction was demonstrated.[8] Monitoring of the early cortical component, however, appears to be more appropriate, because it is less influenced by anesthesia and reflects the arrival of the first volley of impulse at the cortex. Few studies, however, have compared SSEP with EEG monitoring. In a recent study Lam et al[70] found SSEP comparable to conventional 16-channel EEG in assessing the adequacy of cerebral perfusion during cross-clamping of the carotid artery. However, as a predictor of postoperative neurologic dysfunction, SSEP monitoring again was associated with false-positive and false-negative rates. Results from the recently published series on carotid endarterectomy are summarized in Table 3. SSEP appears to be is a reasonable monitor for use during carotid endarterectomy but has no real advantages over conventional EEG.

Cortical Localization

In neurosurgical procedures such as epilepsy surgery or tumor resection involving areas adjacent to the primary afferent areas, exact localization of the sensory motor cortex is essential to minimize neurologic damage. Although the preferred technique is to perform the mapping and resection in an awake patient under local anesthesia with sedation, this is not always feasible or

Table 3. SSEP MONITORING DURING CAROTID ENDARTERECTOMY

Authors/Reference	Year	No. of Patients	False-Positive (%)	False-Negative (%)
Lam et al[70]	1991	64	6	0
Russ et al[121]	1988	149	4	14
DeVleeschauwer et al[154]	1988	156	17	60
Amantini et al[20]	1987	58	2	0
Gigli et al[3]	1987	40	17	0
Russ et al[120]	1985	106	1	17
Markand et al[90]	1984	36	?	?
Jacobs et al[55]	1983	25	?	?

desirable, such as in a child or a very anxious patient. SEPs have been used successfully under general anesthesia to map the sensorimotor cortex in these cases.[2, 84, 154]

Miscellaneous Procedures

Monitoring with SEP has also been used in several other surgical procedures or techniques where the brain or the spinal cord is placed at risk due to potential ischemia. Although monitoring under these circumstances has been found to be useful by the investigators, these indications have not gained wide acceptance and must be considered research and experimental in nature rather than clinical.

Induced Hypotension

Both SSEP and BAEP have been used during induced hypotension for cerebral aneurysm surgery and may be indicated in difficult aneurysms where excessive retractor pressure may have to be used.[26, 50, 61]

Placement of the Patient in the Seated Position

With the awareness that neck flexion in a severely spondylolytic patient may lead to the development of quadriplegia,[53, 94] some have advocated the routine use of SSEP monitoring with such positioning.[50, 53, 94] No substantiating clinical data are available.

Thoracic Aortic Procedures

The spinal cord is placed at risk of ischemia during cross-clamping of the aorta, and SSEP monitoring has been successfully used in these procedures but experience remains limited. In addition, the emergency nature of these procedures often precludes the placement of electrodes and proper recording.[58, 115]

Hypothermic Cardiopulmonary Bypass

Monitoring of SSEP is feasible during such procedures and the CCT has been found to correlate with postoperative neurologic function.[66] In children undergoing profound hypothermic cardiopulmonary bypass, correlation of the rate of return of SSEP during rewarming with postoperative neurologic function has been demonstrated.[17] It is not clear, however, how such monitoring may affect the patient outcome from these procedures.

APPLICATIONS OF INTRAOPERATIVE MONITORING OF MOTOR-EVOKED POTENTIAL

As mentioned previously, although several clinical series assessing the functional utility of MEP monitoring have been published,[64, 74, 76, 159] this technique remains experimental. In addition to the extreme sensitivity of MEP to anesthetic influence, the safety of the technique, electrical or magnetic, has not been established. It is hoped that ongoing research will solve some of these problems, but at the time of writing, neither transcranial electrical nor magnetic stimulation has been approved by the Food and Drug Administration for clinical use. In contrast, monitoring of cranial-nerve EMG is a well-established technique and complements SEP monitoring to decrease intraoperative morbidity in posterior fossa operations.[51, 98, 100, 101]

SUMMARY

The role of intraoperative monitoring of SEP is well established in some surgical procedures, equivocal in many, and probably not useful in others. As the technique and interpretation continue to improve and evolve, so would the surgical indications. With further development and refinement in MEP technology, it will be possible to assess simultaneously sensory and motor functions intraoperatively. Enthusiasm for combined SEP and MEP monitoring, however, must be tempered until substantiated by vigorously conducted controlled clinical trials to establish the influence of such monitoring on patient outcome.

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WHAT EVERY NEUROANESTHESIOLOGIST SHOULD KNOW ABOUT ELECTROENCEPHALOGRAMS AND COMPUTERIZED MONITORS

Ira J. Rampil, MD

The electroencephalogram (EEG) has challenged investigators for over 100 years. These apparently random voltage tracings provide a functional portal into the central nervous system (CNS). Through decades of empiric observation, the EEG has developed into a diagnostic tool, a monitor of cerebral ischemia and anesthetic depth, and a research tool for investigating the pharmacologic properties of psychoactive drugs. A useful analogy exists between the EEG and the electrocardiogram (ECG) because both provide a remote reflection of the electrical activity of millions of organized cells deep in the body. These distant echoes of ionic currents can be used to assess the vitality and function of their originating tissues. The cardiogram consists of patterns that we know represent specific underlying physiologic events and sequences; unfortunately, the EEG provides no deterministic link between waveforms and physiology. Background EEG activity appears to be random tracings having no direct connection to known physiologic sequences. This does not imply that the brain's electrical function is random or chaotic, only that it is so complex and subtle that the EEG appears random.

Historically, the interpretation of EEG required heuristic and visual skills obtained only by years of training in neuroelectrophysiology. The realization that brain waves could be modeled mathematically provided theoretical and

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conceptual support for the mathematical analysis of EEG tracings, which ultimately produced good correlations between mathematic quantitation and various physiologic states, without the continuous, single-minded effort of a trained electrophysiologist. The advent of large-scale integrated circuits then made it possible to introduce the compact, computer-based EEG analyzers that have renewed clinical interest and research in EEG monitoring.

PHYSIOLOGY

The basis of the EEG signal lies in synaptic transmission where the postsynaptic dendrite summates the thousands of afferent signals impinging on it. Axonal transmission contributes little to the genesis of the EEG signal. The release into the synapse of a packet of excitatory neurotransmitter slightly depolarizes the opposing dendritic region. The presence of a small region where the membrane potential (and ionic concentrations) differs from the surrounding membrane creates an electric field in the extracellular fluid. Typically, there is a dynamic balance between depolarizing and hyperpolarizing (inhibitory) transmitters in the synaptic cleft. Over time, the balance shifts from net inhibition to excitation and back, causing the postsynaptic membrane potential to oscillate with the current state. These postsynaptic potentials are relatively long-lasting (tens to hundreds of milliseconds) compared with action potentials, but are individually so small that the electric fields they generate cannot usually be detected at any distance from the cell.

A fortuitous exception to this dynamic exists in the cerebral cortex, where a population of large neurons exists, each possessing a single prominent dendrite, all arrayed parallel to each other and perpendicular to the surface of the cortex (Fig. 1). In a given region of cortex, these pyramidal cells receive many common afferents and their dendrites accordingly tend to have similar postsynaptic potentials. The particular parallel geometry of these cells permits the additive combination of thousands or millions of postsynaptic potential fields, creating in summation a field large enough to be detected at the scalp. This geometry also explains some EEG findings, e.g., when the brain is alert (teleologically requiring the neurons to process diverse afferents), the EEG signal becomes small and the wavelets much faster due to desynchronization of the pyramidal cells. Conversely, when the brain is relatively quiescent, the afferents to the pyramidal cells are more synchronized; therefore, the postsynaptic potentials more efficiently summate, resulting in larger, slower waves.

The high degree of neuronal interconnection in brain can produce interesting or aberrant EEG phenomena. For example, following a neuronal injury, there is often a reduction of neuronal activity in the corresponding area of the contralateral hemisphere. Known as diaschisis, this phenomenon probably is due to the extensive corticocortical pathways crossing the corpus callosum and may contribute to the inaccuracy sometimes apparent in the use of EEG to localize brain infarction.[64]

The EEG is a cortical phenomenon. Consequently, a substantial volume of the CNS neither contributes to nor significantly affects the scalp EEG. For example, hemorrhage in the internal capsule, a common form of cerebrovascular accident leading to hemiplegia, seldom alters the EEG unless the hemorrhage is very large and induces coma.

From its site of origin in the cortex, the electric current associated with the EEG must traverse three "shells" of varying conductance, namely the cerebrospinal fluid, the skull, and the scalp. Postsynaptic potential-derived currents

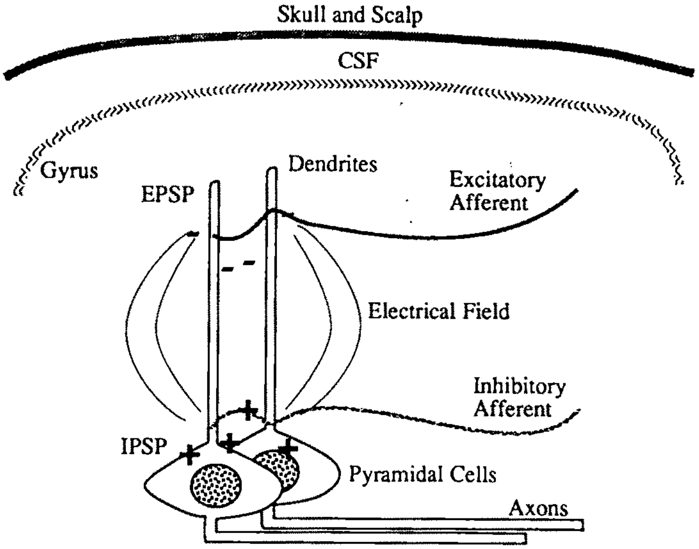


Figure 1. Cortical architecture provides the lattice from which the EEG is generated. Large pyramidal cells, particularly in layer 5, have long straight dendrites that are oriented perpendicular to the cortical surface. Long-latency postsynaptic potentials along the length of the dendrite create voltage differences and therefore current flow along the dendrite. Many thousands of neighboring pyramidal cells have similar postsynaptic potentials allowing the individual current flows to summate to the extent that they can be detected at the scalp.

are blended together in the highly conductive cerebrospinal fluid, forced through the many small and large foramina of the skull, and further blended in the conductive scalp. The effect of these intervening shells attenuates[29] and spatially blurs any focal electrical activity into neighboring areas of the scalp and significantly reduces the resolving power of noninvasive EEG measurements. When a very large number of electrode sites are used, it is possible to mathematically "deblur" the scalp signals with a technique called the Laplacian operator.[55, 70, 136]

ELECTROENCEPHALOGRAM MEASUREMENT SYSTEMS

Electrodes

To be examined by the clinician, the minute currents traversing the scalp must be captured, enhanced, and displayed. The first step is to transduce the scalp currents from ionic form into currents carried by electrons in metal and thence into voltages. This is done by placing pairs of electrodes using a standardized system of sites that uses bony landmarks as reference points for placement[61] (Fig. 2). Electrodes are positioned at points that are 10% or 20% along interlandmark meridians and the system (the International 10-20) provides intrapatient and interpatient repeatability of EEG recordings. Because a voltage is defined as a difference in potential between two points, electrode sites must be considered in pairs. Groups of such electrode pairs are called montages. Many systems of defining and cataloging montages of electrodes exist, many

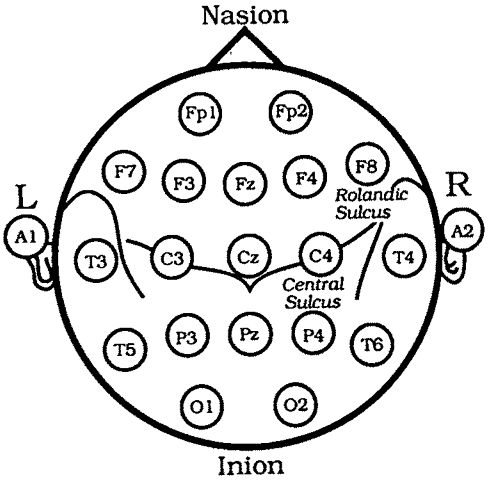


Figure 2. The international 10-20 system for placement of EEG electrodes. This system uses symmetric bilateral placement to detect differences between the two sides of the cortex of any given patient. The essence of the system is that anteroposterior measurements are based on the distance between the nasion and the inion over the vertex in the midline; and five points—frontal pole (Fp), frontal (F), central (C), parietal (P), and occipital (O)—are marked along this line at certain percentages of the nasion-inion distance. This places a central line of electrodes one half the distance from the nasion to the inion. Lateral measurements are then based on the central coronal plane. Even numbers are used as subscripts for the points over the right hemisphere and odd numbers for those over the left hemisphere. Midline electrodes have the subscript z (for zero).

of these were defined empirically and without theoretical (electronic) or logical bases. For a lucid discussion of the "fallacies" in the EEG literature, the reader is referred to the landmark work of Nunez[89] and Katznelson.[66] When multichannel EEG systems are used, a montage consisting of bilaterally symmetric sequential bipolar pairs of electrodes is frequently chosen (e.g., with reference to Fig. 2: FP-1-F3, F3-C3, C3-P3, P3-O1, and FP2-F4, F4-C4, C4-P4, P4-O2).

The role of the electrode is to provide, as nearly as possible, an ideal electrical contact between the patient and the rest of the EEG system (e.g., amplifiers, filters, strip recorders, or computers). The biophysics of electrode interfaces is too complex for this chapter and the interested reader is referred to Geddes and Baker's treatment of the subject.[48] This complex behavior is due to the spontaneous development of a potential barrier at the points of contact of metals with electrolyte solutions. The voltage characteristics of this barrier vary according to the specific combination of metals in the electrode and the electrolyte solution. The combination of silver electrodes with silver chloride solution produces a very stable electrode potential and is the combination most often used. Many other combinations (e.g., stainless steel and saline or extracellular fluid) generate intrinsically unstable potentials, resulting in noise at the electrode interface that may be orders of magnitude larger than the EEG signal. Additionally, the electrode potential is altered by any motion of the electrode–electrolyte junction, creating relatively enormous noise signals. Because of this sensitivity to motion, a common artifact is a rhythmic oscillation in an electrode placed over the superficial temporal artery and "feeling" the pulse. Therefore, the characteristics of an ideal electrode include long-term electrical and mechanical stability, minimal frequency-related distortion, and low electrical contact impedance. It is interesting to note that the latter consideration, the lowest possible contact impedance, was once the sine qua non of electroencephalographers, but it has been rendered passé over the past two decades, as is discussed in the next section.

The electrodes most commonly used for diagnostic (nonsurgical) EEG monitoring are small (about 1 cm) electrolyte cream-filled cups that can be glued to either hairy or bare scalp using collodion-soaked cotton wads. These cup electrodes provide stable, low-contact impedance for prolonged periods, but require time and skill to place correctly. Consequently, they are less than ideal for use by nonspecialists in a busy operating room. A variant of the cream-filled cups is the Electro-Cap (Electrocap International, Dallas, TX), a nylon helmet with cup electrodes sewn into the appropriate sites of the 10-20 system, thereby saving the time required to locate electrodes. Time is still required to abrade the skin below the electrodes, inject the cream, and test the electrodes. Further, a chin strap on the helmet designed to keep the electrodes snug on the scalp would be in the surgical field during extracranial carotid surgery.

For use on a hairy scalp, the primary alternative to cup electrodes are subdermal needles, 30-gauge platinum wires with sharpened tips. The advantage of these needles is that they are quickly and easily placed through any type of skin. The disadvantages include relatively high-contact impedance (due to the relatively small contact area), potential mechanical and boundary layer instability, high cost (unless resterilized and reused), and transient discomfort due to subdermal placement. A good alternative for use on nonhairy skin is the pregelled silver/silver chloride electrodes used in the operating room for ECG. These electrodes are easily available, disposable, and provide stable, low impedance recordings if properly applied. The skin should be prepared for their application by removing surface oils and some of the stratum corneum by abrasion, using either a dry gauze sponge, a rotating pencil eraser, or a small amount of OMNI-PREP solution (a commercially available abrasive, conductive, adhesive liquid, D.O. Weaver, Denver, CO). Electrodes difficult to access intraoperatively should be well secured using tincture of benzoin, Mastisol (Ferndale Laboratories, Ferndale, MI), or adhesive tape. The number and site of the electrodes used for a particular case should be determined by the rationale for monitoring (whether primarily for ischemia or drug effect) and relevant surgical factors such as the site of incision. Many neurologists and others trained in traditional, manually interpreted diagnostic EEG maintain that eight or more channels are mandatory for ischemia monitoring. Others, including this author, maintain that one or two channels of EEG data are preferable to no monitoring, that computer-assisted analysis likely is more sensitive to ischemia than is manual analysis on a per channel basis, and that oligochannel systems are adequately sensitive, even to focal, cortical embolic events.[103] Accordingly, this author suggests routine intraoperative use of two or four channels when EEG monitoring is indicated, especially as the placement, testing, and maintenance of 10 or more electrodes is far too time consuming and distracting from patient care for the anesthesiologist working alone.

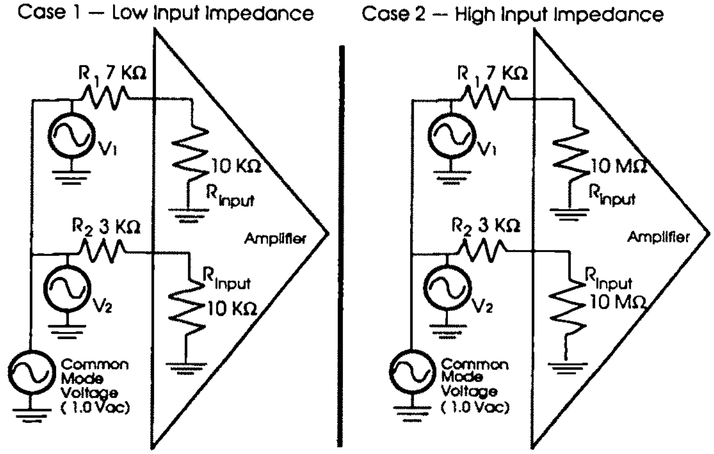
Amplifiers

The amplifiers used for EEG applications are quite similar to those used in ECG; however, the EEG is a smaller signal. The major difference between ECG and EEG amplifiers then, is *gain*, or the amount of amplification. EEG amplifiers usually have a voltage gain of one million (120 dB), while adequate gain for ECG amplifiers is about 10,000.

The other important specification of an EEG amplifier is its input impedance. This is essentially a measure of how much of the current flowing in the scalp is drained into the amplifier. The higher the input impedance, the less perturbation of the biologic source. Early vacuum tube-based amplifiers had input impedances in the range of 10^4 Ω; current designs using integrated circuit have input impedances above 10^7 Ω. This thousandfold increase in input impedance decreases the dependence on carefully optimized electrode contact impedance (Fig. 3).

Differential Amplifiers

The most difficult problem in measuring EEG signals is the presence of "common-mode" noise. This noise is the extraneous collection of undesirable voltages originating, for the most part, outside the patient's body, yet appearing uniformly at all electrode sites. The most frequent source of this type of noise is the AC power network running in the walls of the operating room. The 60- (or 50-) Hz power lines radiate into their surroundings and human bodies act as antennae. Sixty hertz skin voltage from power line coupling to a patient can be orders of magnitude larger than EEG voltages. The best, but impractical, way to eliminate power-line interference is to heavily shield the room where the patient is to be monitored. The next best technique, differential amplification, is the one actually used by essentially all bioelectric amplifiers. Differential


Case 1 — Low Input Impedance
Case 2 — High Input Impedance
R1 7 KΩ
V1
10 KΩ
Rinput
Amplifier
R2 3 KΩ
Rinput
10 KΩ
V2
Common Mode Voltage (1.0 Vac)
R1 7 KΩ
V1
10 MΩ
Rinput
Amplifier
R2 3 KΩ
Rinput
10 MΩ
V2
Common Mode Voltage (1.0 Vac)

$$\text{Common Mode Voltage} = \left(\frac{R_1}{R_1 + R_{input}} - \frac{R_2}{R_2 + R_{input}}\right)$$

$$\text{Common Mode Case 1} = \left(\frac{7}{17} - \frac{3}{13}\right) = 0.1809\text{ V}$$

$$\text{Common Mode Case 2} = \left(\frac{7}{10007} - \frac{3}{10003}\right) = 0.0003997\text{ V}$$

Figure 3. Input resistor chain with CMRR example. When compared with older, low-input impedance amplifiers, integrated amplifiers with very high input impedance are insensitive to minor differences in patient contact impedance. For simplicity, the figure uses only ohmic resistance (R), not impedance (Z). In case 1 with a mismatched pair of electrode resistances, a low-input resistance differential amplifier can only produce a 81.9% decrease in the common mode voltage, whereas in case 2 with the same mismatch, the high-input resistance amplifier produces a 99.96% decrease in common mode voltage.

amplification relies on the observation that common-mode signals (like power-line noise) are equal at all electrode sites, whereas the EEG signal is different at each electrode. Differential amplifiers subtract the signal obtained at one electrode from that obtained at another electrode. The common-mode signal should exactly cancel out, leaving only the voltage difference between the two electrodes, which should be the EEG signal. The efficiency of this noise-cancelling process is defined as the common-mode rejection ratio (CMRR). The CMRR is sensitive not only to the amplifier design (specifically the input impedance), but also to the electrode impedance. Rejection of common-mode artifact can be maximized by attempting to make equal the impedance at all electrodes.

The sensitivity of CMRR to electrode impedance balance is understood by knowing that a current passing through a serial chain of resistors causes a voltage drop across each resistor that is proportional to the fraction of the chain's total resistance contained within the individual resistor (Fig. 3). In making contact with the patient, each lead has two resistances (impedances) in series: the electrode and the amplifier input. In the older vacuum tube-based amplifiers, the electrode impedance (e.g., 5 kΩ) is a large fraction of the amplifier input impedance (e.g., 10 kΩ), resulting in a relatively large decrease in EEG voltage (in this case 33%) available to the amplifier, and a correspondingly high sensitivity of the CMRR to small differences in impedance between different pairs of electrodes. This last effect is due to the fact that when the electrode impedance is a relatively large part of the total impedance, electrode voltage drops are relatively large and therefore if the electrode resistances are not equal, by the time the signals get to the differential amplifier, the common-mode signal is no longer equal in each lead and does not completely cancel out. In current equipment, the electrode impedance (e.g., 5 kΩ) is a much smaller fraction of the amplitude input impedance (e.g., 10 MΩ), resulting in a much smaller reduction in voltage (0.05%) and a proportional decrease in the sensitivity of the CMRR electrode impedance and imbalance.

Filters

Another critical component of an EEG measuring system is the filter. Filters diminish the contribution of electrical activity within specified frequencies while preserving others. The rational use of filters presumes that the information of interest in a complex signal lies in a different range of frequencies from that of the artifact. This often is true of intraoperative EEG signals. Consequently, careful thought should be applied to the filter settings in an EEG system. Most systems have a band pass type of filter that excludes frequencies outside a selectable pass band. If the pass band is set too narrowly, then relevant EEG information will be lost or distorted. If the pass band is too wide, extraneous noise will contaminate the filter's output. In diagnostic EEG recordings, a pass band of 0.5 to 70 Hz is commonly used.[58] However, the increased noise and artifact present in the operating room and intensive care unit, and the decreased high frequency requirements for monitoring (in contrast to diagnosis), dictate a reduction in the filter pass range to perhaps 0.5 to 30 Hz to improve the signal-to-noise ratio.[59]

Diagnostic EEGs are typically recorded on a paper strip chart with 8 to 32 pressurized ink pen channels. The chart is a plot of voltage versus time. Most commonly, recording sensitivity is set so that 50 μV causes the recording pen to deflect 7 or 10 mm. The most common horizontal axis speed is 30 mm • sec^{-1}

or 108 m of strip chart per hour; however, 15, or even 5 mm • sec^{-1} has been advocated as adequate to demonstrate ischemic changes, if not detailed patterns.[120]

ELECTROENCEPHALOGRAM INTERPRETATION

Manual Interpretation

Neurologists examine several aspects of EEG tracings. A prime feature is wave amplitude. EEG waveform amplitude is measured from the peak of a wave to the following trough. The usual range of adult EEG amplitude is from 10 to 100 μV. Interpretation of absolute amplitude values must be tempered by recognition of many possible confounding variables such as electrode impedance, interelectrode distance, the type of electrode montage (discussed later), and the physiologic state of the patient.

Because the EEG voltage is a time-varying signal, it is reasonable to evaluate the rate of voltage change, most commonly by using frequency analysis. Conceptually, this is little more than classifying a segment of EEG as containing slow, medium, or fast waves, or some combination thereof. The first consistent rhythmic patterns detected in the chaos were sinusoidal waves of 8 to 13 cycles per second (Hz) to which Hans Berger gave the name δ rhythms in 1929. Next, he discerned faster rhythms that he classified as β. Later authors added Δ (0–3 Hz), and θ (3–8 Hz) rhythms. To quantify frequency manually, the waves are measured either by measuring the distance between the zero voltage crossing points of an individual wavelet or by counting the wavelets over time (length of total strip chart recording). Because EEG is usually a complex mixture of different frequencies, such manual quantitation can only approximate frequency content; but in most cases of clinical diagnosis, these visual ("eyeball") estimates by an educated observer are assumed to be sufficiently accurate. Although many classic EEG studies are based on this simple four-frequency (α, β, Δ, θ) band analysis, it is important to recognize that there is no physiologic basis for rigidly defined band boundaries. During anesthesia, these strict band descriptions lose their relevance as drugs smoothly shift patterns of electrical activity from β to Δ and back in a reproducible manner. These drug-induced shifts are devoid of the prognostic significance associated with them in the nonanesthesia setting.

Waveshape is another characteristic examined in interpreting EEG tracings. It is generally difficult to ascribe meaning to particular waveshapes in the EEG recording, but there are exceptions. In routine neurologic diagnosis, the most important characteristic waveshapes are those associated with epilepsy. These are spike-like shapes whose exact features are dependent to some extent on the underlying etiology of seizures. In fact, although the definition of a spike is accepted as a sharply pointed wave persisting between 20 and 70 ms, the EEG diagnosis of epilepsy is far more complex and depends on the recognition of such patterns as sudden onset, changes of frequency and amplitude during the ictal event, and postictal depression. Spike waves are not uncommon during enflurane anesthesia. The characteristic waveforms of different types of artifact are perhaps most useful in the operating room setting. The operating room is one of the most hostile environments (electrically speaking) in which an electroencephalographer must work. It combines hazards such as large numbers of patient-connected electronic devices (including monitors and electrosurgical units), the potential for motion artifact, and personnel tripping over cables, thereby demanding absolute vigilance to maintain the quality of incoming signals if EEG monitoring is to be accurate and useful during surgery. A short catalog of artifact waveforms appears in Figure 4.

Clinical (nonsurgical) electrodiagnosis uses eight or more electrodes distributed over the scalp in standardized montages to ascertain regional variations in EEG frequencies and amplitudes. For example, the well-known α rhythm is maximal over the occiput, which helps distinguish it from the equally benign, but less known μ or motor rhythm, which contains similar frequencies but is maximal over the precentral (motor) gyrus.

The EEG response to stimulation is the neurologist's equivalent of the cardiac stress test. The CNS responds to stimuli such as pulsing light and sound; e.g., stimuli normally block the relaxed state α rhythm and cause subsequent desynchronization.

Statistical Basis of Automated Electroencephalogram Processing

Computers can also quantify various aspects of the EEG. To do this, the computer must first translate the time-varying analog signal into a form that it can accept. This is known as digitizing and is performed by examining the signal at a rapid rate, e.g., 125 Hz, and calculating a discrete digital number representing the voltage at each sampling time. For a 1-hour procedure, digitizing at 125 Hz will result in 450,000 voltage measurements. Conventionally, an entire hour of data is not examined as a unit. Rather, to assess EEG data in a timely fashion, the digitized array of data is divided into epoches that are contiguous batches of 250 to 500 samples (2–4 seconds duration) each. An epoch, being a simple array of numbers, can be treated statistically; e.g., a mean or variance can be calculated. The property of stationarity implies that over time (from epoch to epoch) the statistics describing the epoches remain constant. Stationarity is an implicit assumption of many statistical tests.

In fact, in actual biologic systems, true stationarity does not exist. Remarkably, when a subject maintains a constant neurobehavioral state, EEG output does appear to be quasistationary for up to 20 seconds at a time.[60, 74] Stationarity is maintained over longer periods of time during steady-state anesthesia. Some processing algorithms have been designed to sense and adapt to nonstationarity.[13] If quasistationarity was not present, many of our most valuable tools, such as trend-plotting, would be worthless.

Quantitative Electroencephalogram

During the past 50 years, dozens of algorithms have been described to quantify and thereby refine or condense the informational content contained in the EEG. Semantic or syntactic analysis attempts to directly emulate the human observer in recognizing patterns of waveshapes. Statistical approaches use more numerically oriented algorithms. Frequency domain analysis proceeds from the spectral content of an EEG epoch, whereas time domain analysis uses the original voltage waveform. Parametric analysis makes a priori assumptions about the statistical nature of the "underlying generator" to build statistical models of the EEG, whereas nonparametric techniques need no such assumptions. Parametric modeling is a statistical contrivance useful for predicting future activity and for producing sparse descriptions of the EEG state. Para-

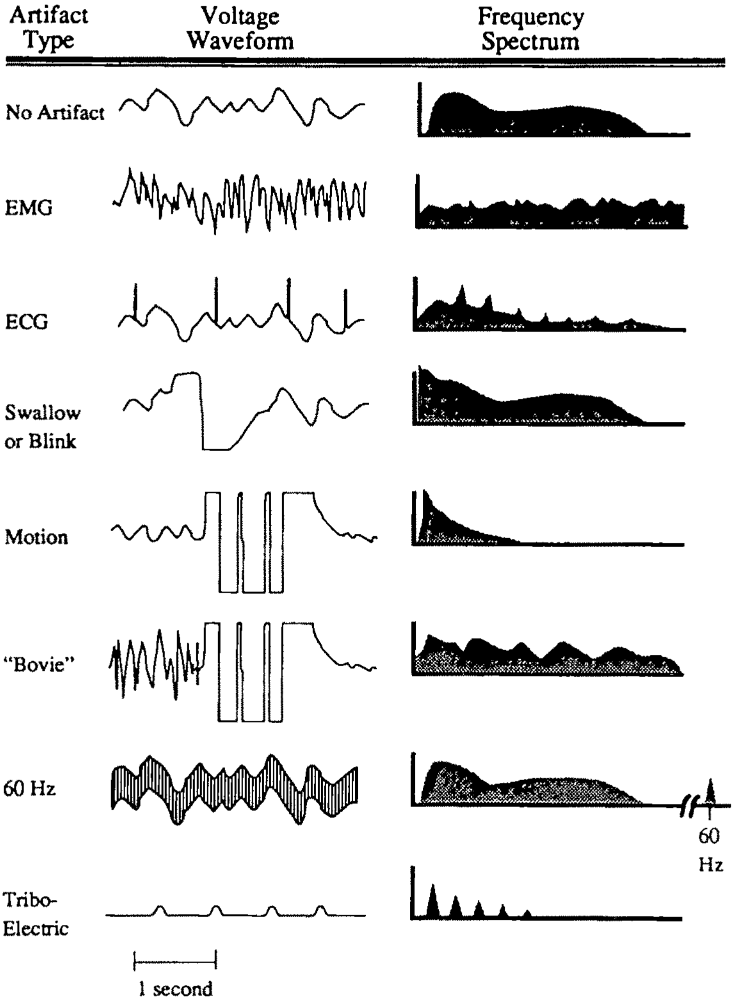


Figure 4. Stylized artifacts are illustrated in both the time and frequency domains. Electromyographic artifact generally adds uniform, wideband (white) noise. Cardiac electrical activity adds a QRS pulse in the time domain that translates to a series of blips in the frequency domain spaced at intervals of the heart rate frequency. Swallows, blinks, and motion artifact are heavily weighted toward delta frequencies. Electrosurgical artifact ("Bovie") when present in small amounts is white noise; if stronger, it saturates the EEG amplifier producing flat line EEG tracings. Power-line interference may significantly distort the time domain waveform, but generally leaves the spectral display unaltered, save a blip at 60 Hz. The triboelectric effect is created by mechanically deforming an insulator around a conductor, e.g., a cardiac bypass roller pump creates the rhythmic pattern in the figure, which is then conducted by the blood into the body.

metric models essentially are digital filters adjusted to take a truly random noise input and produce an output signal that has the same statistical descriptors (i.e., variance, frequency content) as the currently observed EEG. They are not intended to model the underlying physiology. The *parameters* of parametric models refer to the numerical coefficients of the filters that match the model to the EEG. Parametric algorithms are most often applied to diagnostic EEG[79] and have not been successful in real-time applications such as the operating room and intensive care unit. Two factors discouraging their real-time use are the intensive computational load and their nonintuitive approach for clinicians without engineering backgrounds.

Nonparametric algorithms are those that do not use models. They are the most widely used in real-time analysis, with about equal division of popularity between the time- and the frequency-domain algorithms.

Time-Domain Analysis

One of the first[77] quantitative approaches to EEG analysis was the determination of average signal amplitude (a time-domain algorithm), which usually is implemented as the root-mean-square or the mean of the absolute values of the EEG. This measurement is not influenced by the frequency content of the epoch from which it was calculated. In early clinical applications of EEG in the operating room, average amplitude parameters were considered adequate,[10, 16] but it has been empirically observed that EEG amplitude information is not normally distributed, suggesting that statistical comparisons of amplitude data may be inappropriate without first (log) transforming the data toward the normal distribution.[47, 62] This statistical caveat applies to either the whole spectrum or to band analysis.

Zero crossing frequency also is a time-domain algorithm.[18, 69] The assumption inherent in this technique is that most of the significant waves in the EEG waveform will cross the zero voltage axis and thus signify a boundary between waves. The algorithm measures the times between all the zero voltage crossings of an epoch of waveform, finds the mean interval and from it— the "mean frequency." This is actually a crude estimator, because it tends to ignore the contributions of small amplitude waves, which might be superimposed on a larger wave. (Fig. 5). Nevertheless, variants of this technique are simple to implement and seem to provide useful information.[99, 105]

The "aperiodic" algorithm was designed to address some of the shortcomings of the zero crossing frequency. Although related in concept to the zero crossing frequency, the aperiodic algorithm looks for "local" minima and maxima as the boundaries of wavelets, not just zero crossing points. The peak-to-peak amplitude of each wave is retained as well as the interval between adjacent minima (duration of the wavelet).[52] The resulting array of data for an epoch is plotted as a "telephone pole forest" as illustrated by Figure 6.

Another example of a time-domain based parameter is the burst suppression ratio for which the details of computation are given in Figure 7.[108, 109] This algorithm evaluates the proportion of a given epoch representing electrical suppression. The burst suppression ratio can be a useful indicator of electric/metabolic depression due to the depressant effects of drugs such as thiopental, propofol, or isoflurane. Finally, the time domain is the best arena for the automated detection of epileptiform activity as well as many forms of artifact.

The cerebral function monitor (CFM), once popular but now obsolete, was

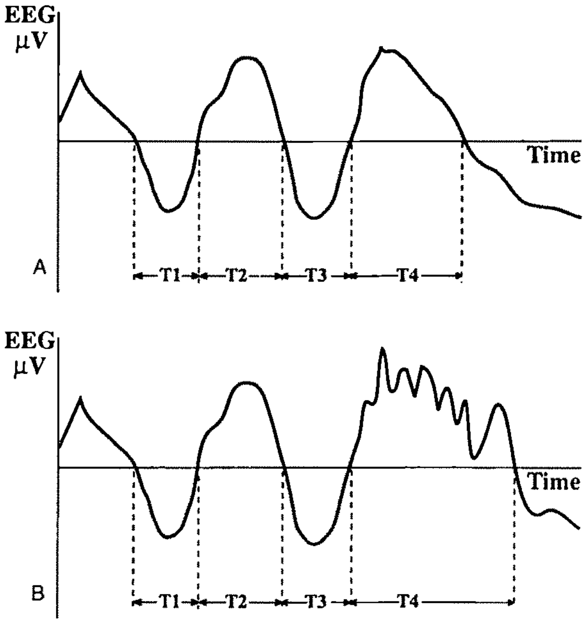


Figure 5. The original zero crossing frequency (ZXF) display simply timed the intervals between sequential crossings of the zero voltage axis. This technique is simple to implement and is an accurate measure of mean frequency when the EEG signal consists of waves that are similar in frequency and amplitude to each other, as in *A*. The zero crossing technique makes significant errors in estimating the mean frequency when the EEG consists of a mixture of wave amplitude and frequency. As illustrated in *B*, small fast waves riding on a larger slow wave do not cross the zero axis and are therefore ignored.

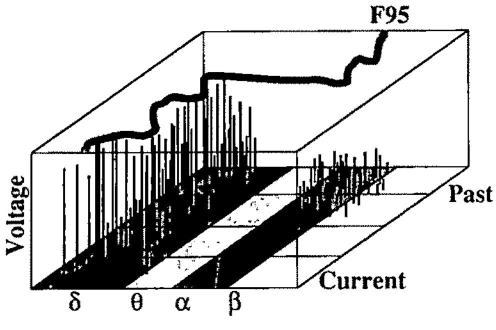


Figure 6. A periodic display as implemented on the Lifescan (Diatek, San Diego, CA). This time-domain display depicts a 4-minute trend in which the newest information is drawn at the bottom of the "close" face of the "glass box." Wavelets are depicted as vertical bars whose height is proportional to the wavelet amplitude, and whose position on the bottom face of the cube is proportional to its frequency band, roughly $\log_{10}$ (frequency) horizontally and recedes in depth with passing time. A spectral edge equivalent (F95) is projected on the top surface of the box. There is activity shown in both the delta and alpha bands until 2 minutes before the current time, when the alpha activity ceased.

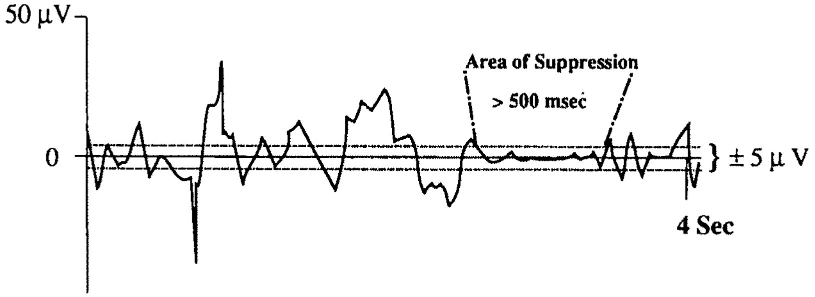


Figure 7. The Burst suppression ratio algorithm is a time-domain analysis technique that quantifies the degree of burst suppression. Scan for contiguous regions where the EEG voltage is < 5 μV. Sum of durations of such regions in an epoch ≡ suppression time. Burst suppression ratio ≡ (suppression time)/(epoch length). (*Modified from* Rampil IJ, Weiskopf RB, Brown JG, et al: I653 and isoflurane produce similar dose-related changes in the electroencephalogram of pigs. Anesthesiology 69:298–302, 1988; with permission.)

based on a time-domain algorithm. This device displayed a single EEG parameter derived from a single channel of raw EEG, via a complex sequence of filtering, logarithmic compression, and rectification. The predominant filter had a rising slope over the pass band (2–12 Hz), thus emphasizing higher frequency activity. This filter produced an output that was the product of the "average" frequency and amplitude within the pass band. There have been anecdotal reports on the application of this device in anesthesia, intensive care, and neurology.[98] Unfortunately, the mapping from EEG input to CFM output was not unique, i.e., two input waveforms with completely different spectra could produce the same output. Specifically, the device could not distinguish mid-frequency, low-amplitude signals from low-frequency, high-amplitude signals. This characteristic rendered the CFM essentially useless for monitoring EEG for changes in anesthetic depth. For example, Sechzer and Ospina[119] found no change in CFM output during 81% of anesthetic inductions with halothane and 91% of inductions with fentanyl. During induction with thiamylal, the CFM increased in 63%, decreased in 10%, and was unchanged in 27%.[119] Moreover, the device was insensitive to β-range frequencies, which are of considerable interest for intraoperative monitoring applications.[32]

Frequency-Domain Analysis

Frequency-domain analysis first translates waveforms that are voltage magnitudes as a function of time into spectra that are voltage or power magnitudes as a function of frequency. This process of conversion is akin to the action of a glass prism, which translates white light into a rainbow of the constituent frequencies. Cooley and Tukey invented the fast Fourier transform, making frequency domain analysis practical for real-time EEG processing.[28, 49] The fast Fourier transform algorithm results in a set of frequency bins, each containing the power of the signal at that particular frequency. Current microprocessor chips can perform real-time EEG fast Fourier transform analysis on up to four or more simultaneous channels. Special-purpose signal processing chips can calculate fast Fourier transforms with even greater speed.

Spectral Displays

Once the spectrum has been calculated for a particular epoch, there are several popular approaches to displaying the data in a useful fashion. At present, the most commonly used is the compressed spectral array (CSA) display technique that was popularized by Bickford et al.[11] The CSA is the now familiar "hill and valley" pseudo-three-dimensional plot of frequency versus amplitude (actually amplitude^2 or power) versus time. A second popular display technique is the density spectral array (DSA) introduced by Fleming and Smith.[45] The DSA uses gray-scale intensity or color changes to represent the EEG power at each frequency in each epoch. The CSA and DSA display essentially the same data, but there are some differences (Fig. 8). The DSA is more compact (i.e., more epochs on a screen) and will not hide potentially important data as the CSA might "behind" high peaks of power. On the other hand, the CSA provides superior dynamic range and resolution of power because it can display hundreds of digital steps in its graph, whereas the DSA usually is limited to 8 or 16 levels of intensity. Either of these display techniques achieves significant compression of EEG information, plotting up to an hour of data on a single screen or sheet of paper instead of the 308 feet of paper required by a traditional EEG recording. This compression eliminates some of the nuances from the raw EEG signal, but the enhanced ability to detect trends is more valuable in the operating room or critical care setting.

Interpretation of CSA/DSA plots still requires an element of pattern recognition. In an effort to simplify interpretation further, perhaps even to the point of automated diagnosis and alarms, many investigators have developed simple numerical parameters derived from the spectral histogram. One simple approach is to divide the spectrum in the classic neurologic frequency bands (i.e., Δ, θ, α, β) and compute (by summing all the frequency bins contained in each band) the total power for each band; the relative power then follows as the ratio of power in a band divided by the total power in all four bands combined.[81] Multiple combinations and ratios of these band powers have been examined and reported. Some recent examples include the augmented Δ ratio, defined as power (8–20 Hz)/power (1–4 Hz), which is reported to be predictive of awakening and responsiveness following anesthesia.[78] The Δ power also has been reported as sensitive to cerebral ischemia during cardiopulmonary bypass surgery.[39] The total spectral power, averaged from 16 simultaneous EEG leads during cardiac surgery (a mixture of open and closed ventricle procedures), was found by Arom et al[2] to predict new global, but not focal, neurologic deficits following surgery.

Another approach to condensing the information in the frequency spectrum is to treat the spectrum as a statistical distribution and use some measure of distributions. Three such descriptors are frequently cited in the anesthesia literature: the peak power frequency,[131] the median power frequency,[31] and the spectral edge frequency (SEF).[102] The peak power frequency is the frequency in the spectrum that displays the highest power in a particular epoch, i.e., the "mode" of the spectrum. The median power frequency is that frequency that bisects the power spectrum, i.e., half the power is below and half above the median power frequency. In statistical terms, the SEF can be compared with the width of the distribution, i.e., that frequency that is two standard deviations out from the mean. In practice, random variations in the spectrum require a pattern matching rather than a strictly statistical approach to obtain a stable measure. The standard automated algorithm is an attempt to emulate the visual recognition of a spectral edge. It searches from the high end of the spectrum

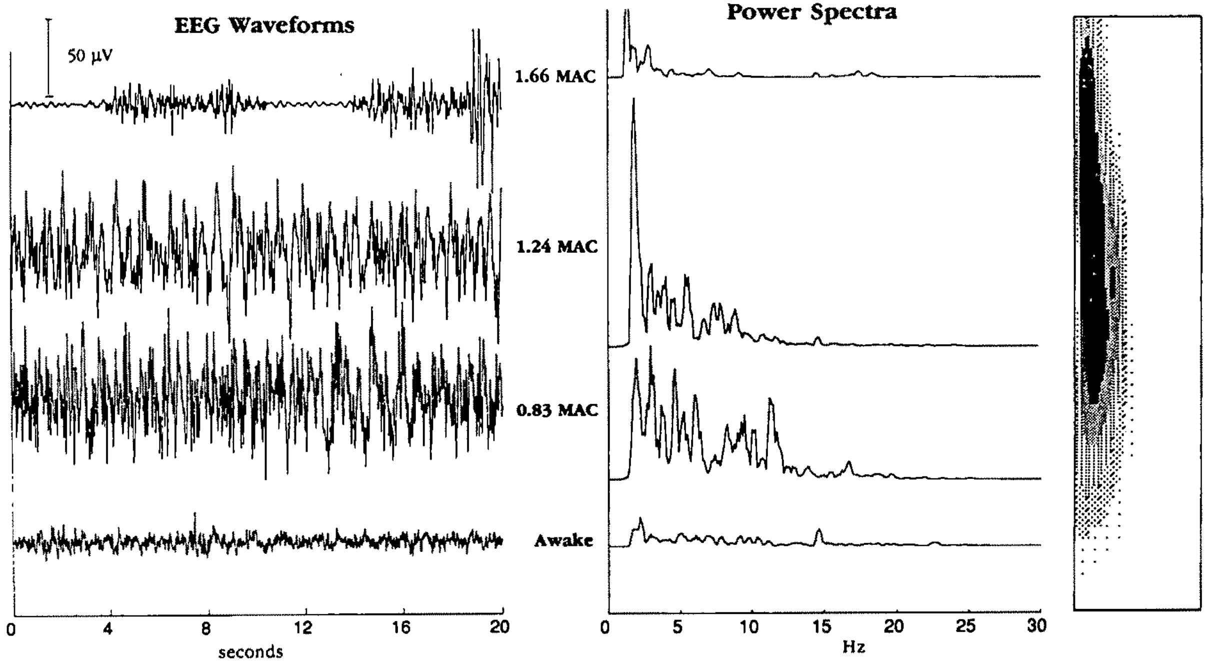


Figure 8. The creation of a spectral array display involves the transformation of time-domain raw EEG signal into the frequency domain via the fast Fourier transform. This process is analogous to the creation of a light spectrum with a glass prism. A spectral histogram is calculated for short collections of sampled waveform known as epoches. The resulting histograms are smoothed and plotted with hidden-line suppression for CSA displays or by converting each histogram value into a gray value for the creation of a DSA display. In this figure, 20 second long epoches (left panel) are acquired from a volunteer at different concentrations of desflurane (data from reference 109). Each epoch is then converted into the frequency domain and displayed in the CSA (mid panel) and DSA (right panel) formats. The width of the DSA panel is 0 to 30 Hz and the changes in DSA pattern along the Y axis (here time, or dose) correspond to the changes in the CSA at the same Y value.

downward, looking for the highest point in the spectrum, which starts a continuous frequency band of EEG activity at least 2-Hz wide, in which each frequency bin (each bin being 0.25–0.5 Hz wide) contains more power than some preset threshold. This approach disregards small random outliers in the higher frequencies. Some investigators have used simple percentile algorithms (e.g., 95th or 97th percentile power) in conjunction with other noise suppression techniques with reasonable success. Another view of the spectral distribution can be had by examining changes in its variance over time.[143]

Levy[75] points out that the EEG is usually complex, may have a multimodal spectrum, and therefore any single descriptor of spectral activity may not reflect the full range of EEG activity, particularly of the appearance of additional modes, or peaks. Whether this conclusion is actually germane to intraoperative monitoring with spectral parameters remains to be answered, because, to this date, there are no clinical or physiologic correlations with the appearance of multimodal versus simpler EEG spectra. In the case of the SEF, the premise and the empiric observations that the highest frequencies are most sensitive to ischemia is not affected by the modality of the spectrum and it is rare that ischemia will be signaled solely by changes in the interior of the spectrum.

Artifact Detection

Electroencephalogram processing is truly a challenge of separating the wheat from the chaff. The problem of extraction of physiologically useful information from a random-appearing EEG signal is compounded by the inevitable contamination by extraneous noise. In this context, noise or artifact is any undesirable signal, e.g., the presence of ECG signal in the EEG leads would be considered noise, because it would interfere with quantification and interpretation of the EEG. There are many sources of such artifacts[106] and most can be controlled using simple preventive measures. Computerized EEG monitors are just as susceptible to the first law of computer science as their larger brethren: *garbage in, garbage out.*

Despite the best precautions in electrode placement, and so forth, artifact will still occur. The presence of artifact need not be considered an entirely negative occurrence because many forms actually contain potentially useful information, which may be extracted from the remaining EEG by sophisticated monitors. For example, a large electromyographic (EMG) signal from the frontalis muscle is commonly seen during light anesthesia. Using band pass filtering, as discussed earlier, the Cerebrotrac (SRD Ltd., Misgav, Israel) monitor separates the EEG and EMG with (usually) minimal cross-interference and provides a separate indicator of EMG activity, which may have its own clinical uses. Some monitors examine the signal amplitude at power-line frequencies, and if it exceeds a preset level, signals the operator to check for poorly connected electrodes. Although many monitors contain limited forms of automatic artifact detection (such as looking for an amplitude exceeding some preset threshold) and flagging, for the present, the best detector is a trained human observer. Nevertheless, automated artifact detection schemes are essential in the processed EEG monitors used in the operating room and critical care settings. The operators of these automated monitors are less experienced in the manual detection of artifact and, more importantly, once the EEG data are transformed into the frequency domain for display as a CSA or DSA, it may be impossible to ascertain the presence of certain types of artifact (while enhancing the detection of other types)(see Fig. 4). Nevertheless, if the EEG signal or its derivatives are being used to adjust patient care, then the EEG waveform data must be audited to ensure that artifactual data are ignored. Ideally, a processed EEG monitor should provide for simultaneous display of both raw (time domain) EEG waves and the processed (usually frequency domain) output in order to ensure a degree of quality control.

Automated Alarms and Diagnosis

A primary rationale for EEG monitoring is the detection of cerebral ischemia. Several guidelines have been proposed as criteria for EEG diagnosis of ischemia, e.g., loss of high-frequency signal activity (a sudden [<30 s] decrease in SEF $> 50\%$, persisting > 1 min)[103] or decrease in overall EEG activity[2] (total power decrease $\geq 60\%$). Such guidelines could easily be programmed into a computer to signal an alarm in response. However, these criteria must first be validated in large, blinded trials, using a variety of anesthetic techniques. Additionally, without appropriate artifact detection and rejection, the accuracy of an automated alarm would be questionable.

The anesthesia workplace has often been compared to the cockpit of an airliner and the anesthesiologist to the pilot in command. Over the initial objections of the pilots, a number of automated warning systems, such as ground proximity alerting, have been placed on airliners, these probably reduce pilot error and save lives. There has been a corresponding desire to simplify EEG monitors to just a warning system. Unfortunately, the analogy to aircraft does not stand scrutiny. By comparison to human physiology, aircraft are simple deterministic systems whose behavior can be completely measured, described, and predicted by a simple system of differential equations. The best such mathematical models of physiology can still only portray the surface layers of complexity and then only in an idealized fashion. Without a firm deterministic underpinning, physiologic alarms must rely on empiric findings. The difficulty here is that the measured variable, EEG, does not necessarily correspond to the underlying cerebral well-being (see following), the EEG itself is stochastic (not at all like a radar altimeter), and the studies showing prognostic clinical value (a reasonable criteria for an alarm) have all been in narrow subsets of patients and anesthetic techniques. The efficacy of such empirically based automated EEG alarms for cerebral ischemia as have been recently proposed for commercial distribution[2, 39] will remain unknown until exhaustive testing has been accomplished.

CLINICAL CORRELATIONS

Awake individuals vary widely in their EEG output, regardless of the means of assessing the EEG. Interested readers are referred to any of the many excellent monographs for details on the subject.[20, 68] In general, EEG data from awake adults contains a mixture of θ, α, and β frequencies, in varying combinations. Anxiety may cause a shift to mostly low amplitude β, while relaxation may result in prominent occipital α rhythms. True (nonartifactual) Δ waves usually are a pathologic finding in awake, unmedicated adults, although normal in the deeper levels of natural sleep.

Intraoperatively, the CNS is sensitive to change in many systemic parameters, including acid–base state, carbon dioxide concentration, temperature, and so forth, that may alter oxygen delivery, metabolic requirements, or afferent neural traffic. Additionally, the CNS responds differently to different types of anesthetic or adjuvant agents and to different depths of anesthesia. Physiologic factors such as age, disease state, electrolyte status also have an effect. Thus, intraoperative EEG has many confounding variables to consider when analyzing the data.

Age

There are developmental changes in the EEG that progress from fetal patterns through senescence. Although specific changes with age are manifest in complex pattern sets, EEG output generally progresses from predominantly slow frequencies in the neonate to higher frequencies through the end of the third decade. Anesthetic potency increases as patients age.[51, 110, 130] At a fixed concentration of isoflurane (1.7%), older patients (78 ± 5 years) had twice the degree of burst suppression as younger patients (28 ± 3 years).[115] Spectral edge frequency has been used as a quantitative measure of maturation of cortical electrical activity in fetal lambs.[134] These differences between child and adult EEG patterns should be carefully considered if intraoperative monitoring is necessary. The literature describing EEG of anesthetized adults is increasing rapidly, but data describing EEG effects in anesthetized children are few, despite a good foundation of information on EEG in awake children. In this author's experience, one may expect to see the same quantitative patterns in children as those described for adults in the following sections.

Carbon Dioxide

EEG changes when arterial carbon dioxide tensions are outside the normal range. During extreme hypocapnea ($P_{CO_2} < 20$–25 mm Hg), cerebral vasoconstriction may reduce cortical blood flow sufficiently to induce ischemia[1] and slowing of EEG output, whereas the intrinsic anesthetic effects of carbon dioxide (CO_2 narcosis) may initially accelerate EEG activity during mild hypercarbia, then slow the EEG while increasing P_{CO_2}[76] leads to deeper anesthesia (the minimum alveolar concentration [MAC] of carbon dioxide is 250 mm Hg in dogs[41]). Rats exposed to supercarbia (P_{CO_2} approximately 400 mm Hg) will have complete or near complete depression of the EEG and will then seize briefly as P_{CO_2} is normalized before reverting to normal function and activity (unpublished observation, Litt L, Rampil IJ, 1988).

Electrolyte Balance

Neuronal function is exquisitely sensitive to electrolyte imbalances that would interfere with synaptic function or impulse conduction. Hypocalcemia is epileptogenic and results in slow background EEG activity with bursts of spikes[72]; frank seizures may occur at serum calcium levels below 6.0 mg/dL.[30] Hypercalcemia is associated with EEG slowing when calcium levels exceed 13 mg/dL.[128] Hyponatremia is also associated with EEG slowing.

Endocrine Disease

The EEG activity appears to be sensitive to circulating thyroid hormone.[97] Hyperthyroidism is associated with acceleration of normal α rhythms, even into the β range, while hypothyroidism is associated with slowing and low-voltage tracings.

Glucose

The brain requires a continuous supply of glucose to function normally. Symptomatic hypoglycemia is associated with diminution of α rhythm, generalized slowing, and may progress to grand mal seizures. Hyperglycemia is associated with little change in EEG unless severe enough to cause obtundation and coma. There is a wide range of minimum plasma glucose levels that are asymptomatic.[145]

Oxygen

The metabolic and functional consequences of oxygen deprivation depend on the circumstances of the episode. Hypoxia is physiologically different from ischemia, and ischemia should be subclassified by whether it is complete or partial, focal or global. Under normal conditions in adults, the brain receives a global average of 50 $cc \cdot 100\ g^{-1} \cdot min^{-1}$ of blood flow and consumes, on average, 3.5 $cc \cdot 100\ g^{-1} \cdot min^{-1}$ of oxygen. When blood flow decreases below 40% (about 20 $cc \cdot 100\ g^{-1}$) of normal or arterial hemoglobin saturation falls below 60%, the electrical activity of the neurons becomes depressed.[63] When cerebral blood flow falls below 25% to 30% of normal (about 12–15 $cc \cdot 100\ min^{-1}$), electrical activity ceases, although the cells remain metabolically viable, at least for some period of time. At cerebral blood flow values below 20% of normal, cellular damage occurs quickly, i.e., 4 to 5 minutes at normothermia, unless cerebroprotective agents are being used. If sudden ischemia occurs, e.g., as may during a cardiac arrest or carotid artery clamping, EEG activity will begin to change within 15 to 30 seconds.

The pattern of EEG change with hypoxia or ischemia may vary according to the type and severity of insult, but, typically, the pattern progresses from an initial loss of high-frequency activity to an increase in relatively synchronized δ activity, and, finally, a decrease in the amplitude of all activity. Prompt restoration of blood flow and substrate supply will generally restore EEG activity to normal. A typical ischemic pattern is shown in Figure 9. Recently, Clute and Levy[26] examined the EEG during 93 episodes of brief, intentional cardiac arrest in 10 patients anesthetized with volatile anesthesia. They found that the EEG detectably changed in only 88% of asystolic episodes, but that of those, 93% had "classic" changes involving acute slowing (to δ or θ). The other episodes were characterized by an isolated loss of δ activity, with preservation of higher frequencies. Restoration of oxygen transport after the onset of neuronal damage, i.e., in the case of a mature stroke results in a spectrum of EEG patterns ranging from slight diffuse slowing of normal activity, frontal intermittent rhythmic δ activity (FIRDA pattern), epileptiform activity, monotonic, nonblockable α rhythm (α coma), or electrocerebral silence.

Ischemia of white matter (i.e., capsular stroke) may not lead to significant EEG findings. The territorial boundaries of the major arterial supplies to the brain are known as watershed areas and the cerebral cortex in these areas are thought to be particularly sensitive to ischemia resulting from reduced cerebral perfusion pressure. Despite the anatomic localization of these watersheds, the EEG findings following acute watershed ischemia frequently reveal ipsilateral

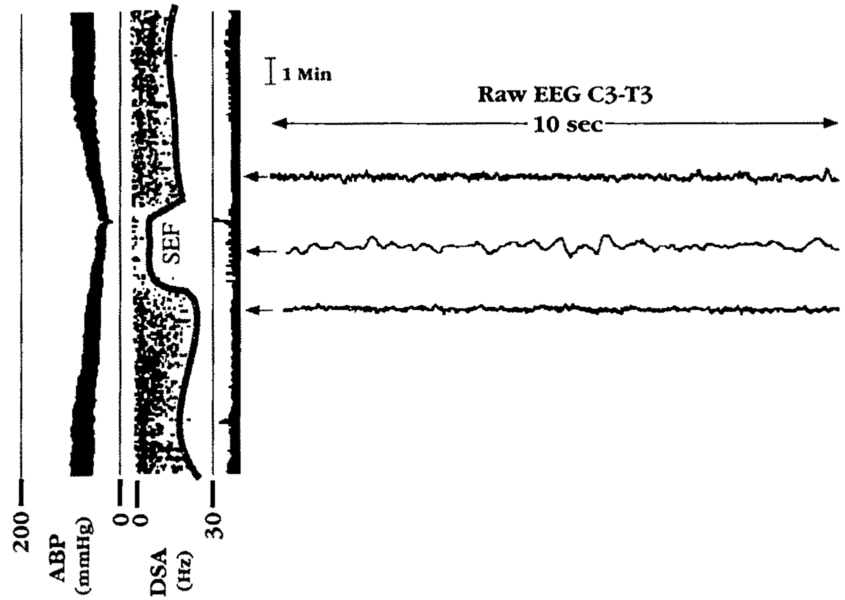


Figure 9. An example of ischemic changes as portrayed by a density spectral array display. In this case, the recording begins at the bottom of the figure and ends at the top, a total of just over 17 minutes. The raw EEG tracings on the right side of the figure correspond to the activity present at the time in the DSA tracing at the same vertical level of the graph. The initial spectral edge frequency (drawn in gray) is in the range of 20–25 Hz, compatible with the moderately light halothane-fentanyl anesthetic. The arterial pressure decreases slowly until the systolic pressure is 80 mm Hg. At this point, the EEG changes with a complete loss of alpha, theta, and beta activity and retains only intermittent delta. The spectral edge falls from 20 to less than 5 Hz in less than 1 minute. When, after 3 minutes of ischemia, the blood pressure rises above 80 mm Hg, the EEG activity promptly returns to its baseline pattern. It is noteworthy that the raw EEG tracings are separated by 11 pages of strip chart, whereas the corresponding tracing of the DSA required 3 inches of paper for the same period of time.

hemispheric slowing, often accompanied by spike waves.[88] The concept of using EEG to monitor for excessive hypotension developed with Beecher et al,[8] who noted that feline EEG activity changed with hypotension. EEG may be useful in monitoring the adequacy of cerebral perfusion during surgery benefiting from induced hypotension, such as total hip arthroplasty in elderly patients with impaired cerebral autoregulation.

Systemic hypoxemia progressively but reversibly slows EEG activity. The EEG appears to change sooner than brain stem auditory evoked potentials in rabbits subjected to hypoxic hypoxia.[95] Persistent hypoxemia leads to EEG silence followed by neuronal necrosis. EEG, however, is not an effective substitute for pulse oximetry because significant EEG changes do not occur until the arterial hemoglobin saturation falls below 60%[27] in awake subjects. With the gradual onset of hypoxemia, EEG activity may transiently accelerate before slowing. This excitation is thought to be secondary to increased afferent traffic from peripheral chemoreceptors.[57]

Temperature

Hypothermia causes progressive slowing and diminishes the amplitude of EEG activity.[17] During cooling, there is a linear relationship between tympanic membrane temperature and quantitative EEG analysis, such as spectral edge frequency.[77, 112] Depending on the type of concurrent anesthetic, the frequency-domain patterns will vary, as will the temperature at which electrical activity will cease. Patients undergoing cardiopulmonary bypass with moderate hypothermia (28–30°C) will usually have a sufficiently active EEG in which changes suggestive of cerebral ischemia can be detected, whereas deeply hypothermic patients (<20°C) may have EEG activity so depressed as to render it useless for ischemic monitoring. EEG monitoring to determine the point at which electrocerebral silence occurs has been suggested as a more meaningful indicator of cerebral metabolic depression than core temperature monitoring in circulatory arrest surgery.[85] Hypothermia prolongs thiopental-induced suppression of cortical activity.[101]

DEPTH OF ANESTHESIA

The relationship of depth of anesthesia to EEG is well described empirically, but varies greatly between patients and between different anesthetics. Practical application of the EEG to monitor anesthetic depth is complicated by the lack of usable definitions for depth. Far from Guedel's unitary set of epiphenomena to represent anesthetic depth, most clinicians now recognize at least five (not necessarily correlated) components of anesthetic effect: analgesia, unconsciousness, amnesia, depression of autonomic responses, and muscle relaxation. Of these, only muscle relaxation can be directly, continuously, and unambiguously assessed; yet most clinicians would not consider the state of muscle relaxation or EMG to be a definitive indicator of anesthetic depth.

Another approach to testing the adequacy of anesthesia is provocative, i.e., to test a patient's response to stimulation. Unfortunately, there are still too few data on the possible correlations between EEG and the major responses to stimulation: movement or lack thereof as an indicator of adequate anesthetic depth (i.e., MAC) or changes in autonomic activity (MAC-BAR or hemodynamic). The correlation is complicated by the fact that noxious stimulation changes the EEG. Usually, incision will increase EEG activity; paradoxically in some patients, the EEG will slow to δ in the EEG equivalent of a vasovagal reaction. Dutton et al[37] has demonstrated that a variant of spectral edge frequency (F95) was a more accurate predictor of movement with surgical stimulation (average probability, 81%) than arterial blood pressure (average probability, 66%) or heart rate (average probability, 60%) in 300 young women receiving isoflurane with various combinations of nitrous oxide and fentanyl. There is also a predictive relationship between EEG spectral edge and arterial blood pressure response to laryngoscopy after a thiopental-fentanyl anesthetic[107]; patients with slow EEG (SEF < 14 Hz) had smaller increases in blood pressure than patients with spectral edge frequency greater than 14 Hz. Whether this relationship between EEG and the response to stimuli will be found when using other anesthetic drugs is uncertain. Sidi and colleagues[122] found that titrating fentanyl to a spectral edge frequency of 10 Hz or less produced less hypotension with less fentanyl required than a standardized dose of 50 μg/kg. Withington et al[140], however, was unable to correlate a variant of spectral edge with drug concentration during methohexital infusion. In lieu of physiologic correlations, most investigators have used pharmacologic correlations. EEG responses to serum or end-tidal drug concentrations have been plotted for many drugs and, although useful, this technique may result in poor correlation between concentration and the gold standard of response to stimulation because of the potentially wide range of drug sensitivity in a population.

In 1959 Martin and his colleagues[80] provided a useful template of the EEG dose response to general anesthesia. This template, contained in Figure 10, was originally developed for ether anesthesia and extended to thiopental, but still contains several important lessons for current anesthetic and monitoring practice. The original curve represented the biphasic change in EEG power with changing levels of thiopental anesthesia. The curve illustrates that awake EEG is very variable between individuals and in an individual over time. Light anesthesia is associated with brain stimulation and an increase in EEG activity, corresponding to the excitement phase. Finally, as anesthesia deepens, the activity and the interindividual variability diminishes. At high concentrations of general anesthetics, brain activity becomes intermittent, a pattern known as burst suppression, and finally isoelectric. An update of this curve (Fig. 10), based on the author's experience, reveals the same general shape of the curve despite the change to a frequency-domain–based EEG parameter. Current clinical practice includes narcotic anesthesia and the narcotic curve is superimposed, as is a curve representing the actions of some anesthetics that activate EEG activity. The following sections discuss some the specific EEG patterns seen with the currently favored selection of drugs.

Detection of intraoperative awareness is a potential application of EEG monitoring.[96] Awareness and recall represent a continuum ranging from completely awake (and possibly paralyzed) to subconscious recall of auditory messages. Generally, during emergence from anesthesia the EEG reverses the pattern set during induction by increasing high-frequency activity. However, reliable correlation between a patient's EEG and that patient's propensity to

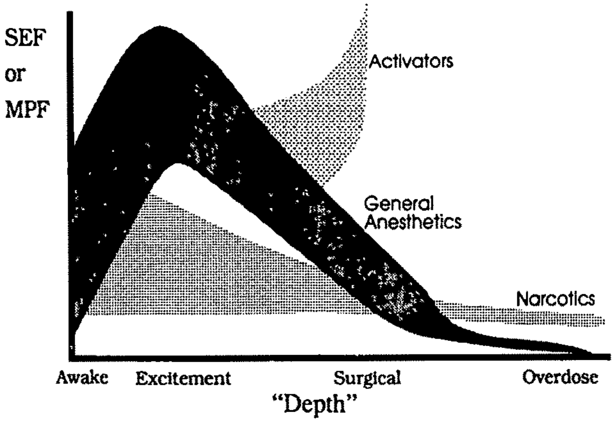


Figure 10. General template of anesthetic effect on EEG. The original template of Martin, Bickford and Faulconer showed a biphasic change in EEG power with a decreasing population variance as depth increased. This pattern is still valid with current anesthetics and frequency domain quantitation of EEG. Activators of EEG, such as ketamine and enflurane may cause seizures at a depth beyond the excitement phase. Narcotics have a sigmoidal effect where very small doses cause no change and very large doses have a ceiling to their response which is short of complete EEG suppression.

awareness or recall has yet to be established. Preliminary results of a study in patients and volunteers at the author's institution revealed no correlation between quantitative EEG measurements and a patient's recall of an auditory message, or the patient's tendency to move in response to surgical incision (unpublished data, Dwyer R, Rampil JJ, 1991). Some investigators have sought an EEG parameter that might predict the onset of ability to follow commands during emergence.[78]

Volatile Agents

Induction with halothane,[91, 94] enflurane,[87] isoflurane,[25, 40] sevoflurane,[113] or desflurane[109] all are associated with the loss of occipital α rhythms and the genesis of frontally maximal, relatively well-synchronized β activity. This activity may resemble sleep spindles or a fast version of α rhythm. In a spectral display, it will create an α-β band of activity, usually separated from the δ activity by a region of spectrum containing little activity. Once this anesthetic-induced fast activity appears, its dominant frequency changes inversely with the anesthetic concentration and spreads its distribution over the scalp. This archetypal drug-induced fast activity invites comparison with, but it should not be confused with, α pattern coma, a postischemic or trauma pattern heralding a very poor prognosis. At surgical levels (> 1.0 MAC), the volatile anesthetics begin to differ in their EEG effects. Isoflurane and desflurane begin to induce burst suppression above 1.2 MAC, without further slowing of the activity within the remaining bursts. Enflurane is associated with epileptiform activity,[87] particularly spike and wave complexes or even frank seizures above 1.5 MAC. Halothane causes a reasonably linear monotonic slowing in the fast activity easily noted in the spectral response to sinusoidal variation in halothane concentration (Fig. 11); burst suppression does not occur at clinically relevant concentrations of this drug. Intense noxious stimulation by tetanic stimulation of the sciatic nerve of dogs receiving less than 1 MAC of halothane activates EEG (desynchronization) and increases $CMRO_2$ but provokes little change in dogs receiving more than 1 MAC.[71] Similar changes have been reported in adult humans following skin incision, whereas stimulation in children anesthetized with halothane tended to produce high-voltage slow waves.[91]

Nitrous Oxide

The effects of nitrous oxide on the brain depend on the circumstances of its administration. Given alone, in subanesthetic concentrations (up to 70%), Yamamura et al[142] found that nitrous oxide induced a frontally dominant, fast rhythmic activity having an average peak frequency of 34 Hz. Traces of this fast oscillatory activity persisted for up to 50 minutes following nitrous oxide exposure. When combined with other volatile anesthetics, nitrous oxide usually increases the amplitude and frequency of the anesthetic-induced fast activity in dogs[125] and rabbits.[65] Avramov et al[3] have reported that when nitrous oxide was administered to humans receiving a steady-state concentration of halothane, the sequence of EEG patterns over the course of approximately 1 hour changed in a manner suggesting the development of tolerance to the nitrous oxide.

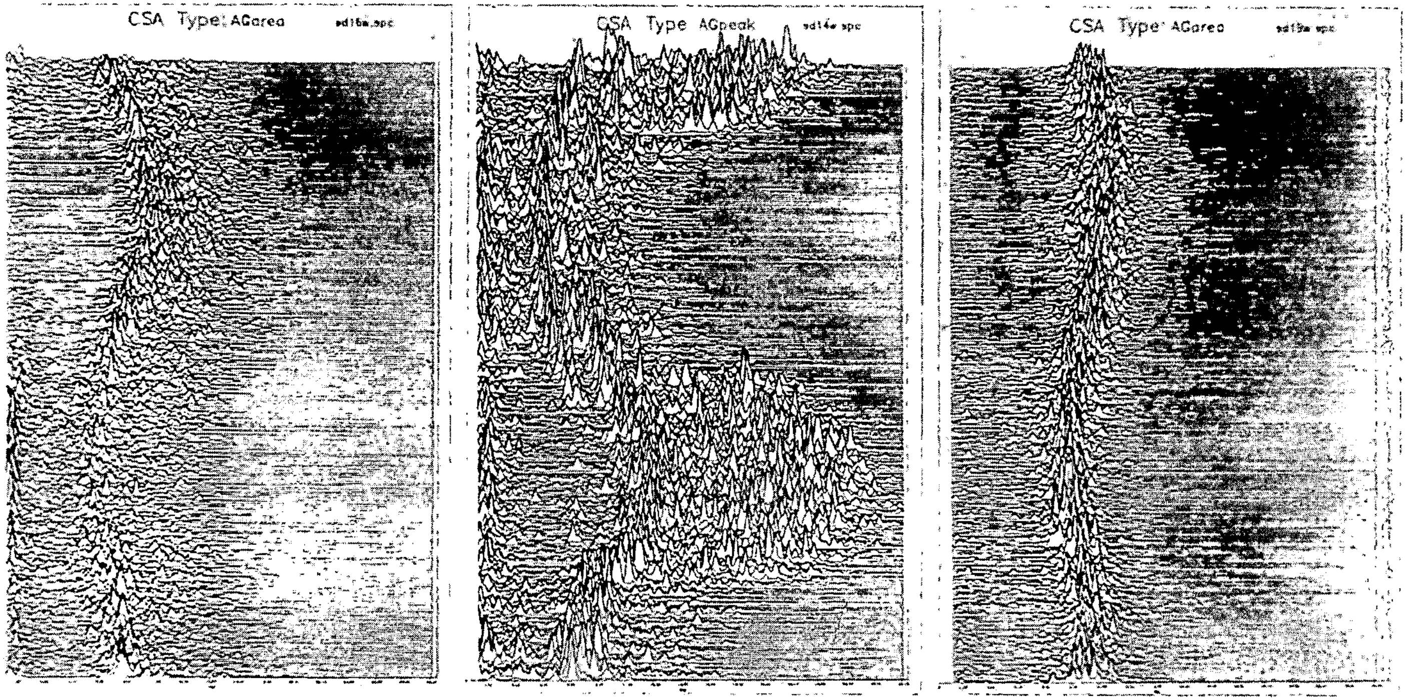


Figure 11. Sine wave response apparent in the compressed spectral arrays of three healthy male volunteers given a sine wave variation (period of 31 minutes, concentration varying from 0.5% to 3.0% in oxygen) of halothane. The sinusoidal appearance of the responses implies a linear dose response; however, there is a wide inter-subject variation in the slope of the response curve. (Data courtesy of Dr. N. T. Smith.)

Barbiturates

Barbiturates follow the drug response template: small doses cause drug-induced fast activity that is similar to that apparent with other general anesthetics, while higher doses increase EEG depression, culminating in burst suppression, then electrocerebral silence if the dose is high enough.[24, 67] There appears to be a topographic sequence of EEG changes (Fig. 12) similar to those seen with volatile anesthetics. The appearance of the fast activity corresponds with clinically apparent excitement phenomena and insensibility results when substantial δ activity is present.[24] The straightforward pattern of EEG power during barbiturate anesthesia was used by Bickford[10] in the late 1940s to automatically control thiopental anesthesia in surgical patients, then later by Cosgrove and Smolen[31] in rabbits. Schwilden and colleagues[116] have reported using median power frequency to control methohexital sedation in volunteers, but although it was possible to maintain a steady median power frequency of 2 to 3 Hz, this EEG pattern was not clearly correlated with an acceptable anesthetic state. Methohexital is interesting in that while it is a potent anticonvulsant like the other barbiturates, it actually enhances interictal epileptiform activity in predisposed patients, whereas thiopental does not.[92] Therefore, it is useful in localizing seizure foci during epilepsy surgery.[46, 141]

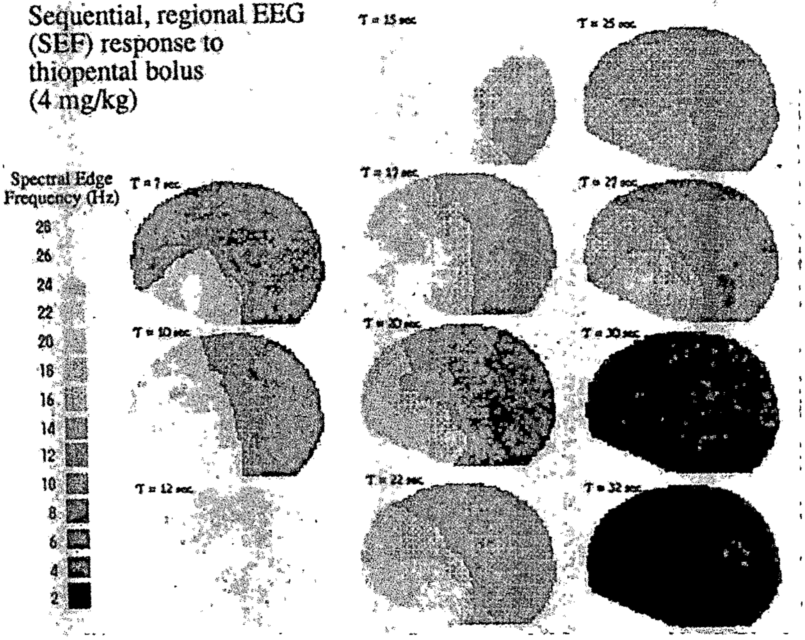


Figure 12. A sequence of "snapshots" at 2.5 second intervals displaying the changing distribution of EEG frequency content (in this case, Spectral Edge Frequency) over the scalp following a bolus injection of 4.0 mg/kg thiopental. In frames T=7 through T=17, there is a prominent focus of frontotemporal fast activity which spread posteriorly during this interval. Starting at about T=15, extreme slowing and suppression begins occipitally and spreads anteriorly, enveloping the entire cortex by T=30.

Etomidate and Propofol

Etomidate causes changes in EEG similar to those induced by barbiturates.[35] Like methohexital, in small doses (0.1 mg/kg) etomidate enhances interictal activity of epileptic foci,[38] although the myoclonic activity occasionally observed during induction with this drug in nonepileptic patients is not associated with cortical epileptiform activity.[35, 49] In higher doses, etomidate causes burst suppression and a reduction in $CMRO_2$ similar to that seen with thiopental.[84] The cerebral metabolic depression and relatively preserved hemodynamic stability associated with etomidate may confer cerebral protection during temporary occlusion for aneurysm surgery.[7] Etomidate also has the interesting property of increasing the amplitude of somatosensory evoked potentials.[82] Propofol appears to induce the same EEG pattern of excitement followed by depression and culminating in burst suppression as the barbiturates.[53] Like etomidate, induction with propofol is sometimes accompanied by spontaneous, dystonic movements. These movements are coincident with the onset of EEG slowing to δ range, and not with epileptiform activity.[14]

Ketamine

Ketamine is a dissociative agent that provides a different EEG pattern than the general anesthetics. The onset of sedation results in a high amplitude, rhythmic θ activity, often accompanied by a significant increase in β-range activity.[114] Ketamine can provoke frank seizure activity in patients with epilepsy, but only rarely in normal subjects.[86]

Narcotics

The EEG effects of narcotics differ from those of the general anesthetics, as illustrated in Figure 10. Generally, there is little or no excitement phase when μ-subtype agonists (morphine, fentanyl, sufentanil, alfentanil) are administered, but instead, a steady decline in frequency content until only δ activity remains.[21, 118, 138] There is no further change in the EEG with increasing dose. Burst suppression does not occur with narcotics. Peripheral muscle rigidity is not associated with cortical seizure activity,[9] but rather seems to be a direct effect of narcotics on an area of the brain stem, particularly nucleus raphe pontis.[139] Seizures are not seen during clinical administration of narcotic anesthesia, but have been noted in dogs given extremely high doses (4 mg/kg intravenously) of fentanyl[33] and in the presence of normeperidine, a metabolite of meperidine.

Benzodiazepines

When used in small doses as premedicants, or as adjuvants to induction of anesthesia, benzodiazepines induce significant, predominantly frontal β-range activity.[50] Increasing doses are associated with generalized slowing to the θ/δ range, apparently without burst suppression.[44] Flumazenil promptly restores EEG activity to a prebenzodiazepine state.[44] Aside from their salutary effects on patients, premedication with a benzodiazepine frequently simplifies EEG interpretation during induction and maintenance of anesthesia because additional anesthetics cause only a decrease in EEG frequency content. Diazepam is widely used as an anticonvulsant, but it does induce fast activity and possibly even spikes in patients with epilepsy.

Muscle Relaxants

Although succinylcholine is not usually thought to affect the CNS, intravenous bolus administration appears to cause an increase in EEG activity and cerebral blood flow resembling arousal and persisting far longer (5 minutes) than might be expected from EMG fasciculation artifact.[73] Lanier and colleagues[73] hypothesize that this effect is due to increased afferent neural traffic from intrafusal fibers in fasciculating muscle.

Atracurium is metabolized to a large extent by nonenzymatic Hofmann elimination. One of the metabolites of this process is laudanosine, a compound long known to be a convulsant and cerebral stimulant.[4, 19] Although it is unlikely that a patient will receive a sufficient dose of atracurium intraoperatively for laudanosine to cause convulsions, administered doses may be sufficient to increase EEG activity and perhaps alter the depth of anesthesia.[121]

ISCHEMIA MONITORING

Monitoring patients at risk for focal ischemia presently is the most important indication for EEG monitoring. As indicated earlier, the EEG provides a convenient indicator of failing cerebral function that can permit timely therapeutic intervention that may prevent or minimize neurologic damage. The best documented demonstration of this principle is the use of selective shunting during carotid endarterectomy.[6, 12, 23, 56, 93, 137] Sundt and his colleagues[132] compared regional cerebral blood flow (intracarotid[133] xenon injection with a single detector over the ipsilateral sensorimotor cortex) and continuous surveillance of 16 raw EEG tracings by a neurologist, with patient outcome in a large clinical series. They found that all major, new postoperative deficits were preceded by intraoperative EEG change, and that the EEG changes correlated with regional cerebral blood flow measurements. In 1979, Chiappa et al[22] compared a raw eight-channel EEG monitoring routine with a four-channel compressed spectral array display and concluded that the latter ". . .proved to be of greater utility than did routine EEG methods." In 1983, Rampil and colleagues[103] defined specific criteria with which to diagnose the occurrence of ischemia (rapid drop in spectral edge frequency of > 50%, persisting 10 minutes or longer) and found it to be useful in predicting new postoperative neurologic deficits in preoperatively intact patients undergoing carotid endarterectomy with general anesthesia. Russ et al[111] and Baker and Roxburgh[5] found similar results with these criteria. Abnormalities present in the EEG of patients with preoperative stroke rendered the aforementioned criteria less useful in those patients.[103] For all the reasons previously described, EEG monitoring cannot be expected to have 100% sensitivity and specificity, as the occasional case report will attest to.[15] A recent report notes that during carotid surgery with cervical plexus regional block, computerized EEG monitoring using criteria developed for general anesthesia may not be accurate.[123] Given the variability of EEG in awake patients noted in Figure 10, this result is not surprising. Given that ischemia of many, perhaps most, subcortical areas would produce no detectable change in EEG, it is fortuitous that monitoring during anesthesia is as sensitive as it appears to be.

Despite its putative accuracy, the utility of EEG monitoring during carotid surgery is a matter of debate as exemplified by the opposing editorials of Ferguson and Sundt.[43, 133] EEG should only be considered useful in patient care if it could be used to initiate and control therapeutic maneuvers for the treatment of ischemia. Three such maneuvers have been proposed: selective intraluminal shunting, induced arterial hypertension, and barbiturate protection. Shunting provides some degree of continued perfusion during carotid artery clamping at the risk of increased embolization. It would therefore be prudent (in theory) to place a shunt only in those patients whose brain indicates a need for additional perfusion following carotid clamping. The efficacy of computerized EEG-based selective shunting was recently examined by Tempelhoff et al,[135] who used as diagnostic criteria either the spectral edge decrease of 50% or greater[103] or a decrease in total EEG spectral power of greater than 30%. When selective shunting was used, EEG remained a useful predictor of postoperative outcome, yet the question of whether EEG-based selective shunting improves patient outcome remains unanswered. For example, a shunt placed during persistent EEG changes indicative of ischemic does not ensure resolution of the ischemia.[104] Prospectively elevating arterial blood pressure with phenylephrine during this operation is a maneuver that appears to triple the risk of myocardial ischemia.[124] EEG may therefore be useful to "titrate" the demands of the brain against the workload of the heart, although, at present there are no data to confirm this patient management technique. Finally, evidence of cerebral ischemia may prompt one to consider administration of thiopental,[54] but again the evidence is as yet inconclusive with respect to controlled clinical trials.

The advent of cardiopulmonary bypass and interest in what that particular physiologic trespass did to the brain was an early motivating factor in the development of intraoperative EEG monitoring. As neuropsychiatric testing has become more sophisticated and widespread it is clear that there is a high risk (up to 60%) of damage following cardiopulmonary bypass. In a prospective study of 65 patients, Soltaniemi[126] found that 37% developed new (mostly transient) neurologic deficits within 10 days of surgery and an additional 21% who were neurologically asymptomatic had pathologic EEG changes.

In 1981 the National Center for Health Care Technology (Office of Health Technology Assessment) of the Department of Health and Human Services formally assessed the literature and solicited comments[117] from device manufacturers, physicians, and other interested parties regarding the value of intraoperative EEG monitoring during cardiac surgery. The resulting report[100] concludes the following:

> *There is little published data based on well-designed studies regarding the clinical effectiveness of brain wave monitoring during open-heart surgery. . . . It appears that there is no clear role for routine EEG monitoring during open-heart surgery and in the immediate postoperative period for patient management.*

In the decade since this report was written, little has changed with respect to data objectively supporting the use of intraoperative EEG monitoring for cardiac surgery. Soltaniemi, examining only preoperative and postoperative EEG records of 49 cardiac valve replacement patients with 5 years of follow-up, found correction of preoperative circulatory abnormalities resulted in improved EEG and neuropsychiatric outcomes[127] and that there were more abnormal quantitative EEG scores in the patients with neuropsychiatric impairment than in those with neuropsychiatric improvement. There have been several reports of the direct intraoperative utility of EEG monitoring, e.g., case reports citing EEG detection of cerebral ischemia that might have otherwise gone undetected, one involving an aortic cannula dissection,[83] another involving a pump malfunction,[42] and yet another involving vertebrobasilar arterial kinking.[129] Nussmeier et al[90] used EEG to titrate sufficient doses of thiopental during normothermic cardiopulmonary bypass to effectively reduce postoperative neuropsychiatric deficits. Zaidan et al[144] also used EEG burst suppression to titrate thiopental during hypothermic cardiopulmonary bypass but did not find any benefit in thiopental administration. Finally, Arom and colleagues[2] claim a reduction of postoperative neuropsychiatric deficits when using increases in total power in a 16-lead montage to diagnose and actively treat presumptive cerebral ischemia during cardiac surgery. Independent verification of the beneficial results of the latter report is eagerly awaited by clinicians hoping to use EEG monitoring to improve patient care.

THE FUTURE OF ELECTROENCEPHALOGRAM MONITORING

At present, EEG monitoring is neither popular nor widespread. There are many reasons for this failure to penetrate into routine practice, including the additional expense and complexity of the equipment and a lack of training and education. Perhaps the central reason, however, is that EEG monitoring has yet to be proved as a positive addition to patient care. Most nonsurgical, perioperative morbidity and mortality in recent years has been due to hypoxia, and although as yet unproven, pulse oximetry and capnography provide an direct, elegant solution. Likewise, the effects of anesthetic overdose are due in large part to hypotension, and arterial blood pressure is similarly the direct variable to monitor. As yet there are no data to support EEG monitoring to prevent anesthetic underdose and intraoperative awareness. The detection of cerebral ischemia would seem to be a reasonable goal in high-risk procedures, but most of the ischemic etiology is related to surgical technique or emboli. Diagnosis of ischemia must be imperfect because of the relatively large volume of electrically silent tissue and the depressing or confounding effects of anesthetic drugs. The sensitivity and specificity of the diagnosis of ischemia may be significantly improved by the combination of EEG with a metabolic monitor such as near infrared transcranial oximetry. Once the diagnosis of cerebral ischemia is made, there are no proven retrospective therapies, although general supportive measures may be useful. Should any of the very active lines of research in brain protection and resuscitation (i.e., calcium channel antagonists, excitotoxin antagonists, free radical scavengers, and so forth) develop into clinically useful therapy, then EEG monitoring may become truly useful and used.

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Glossary

α Band	A spectral range of frequencies from 7 to 13 Hz.
α Coma	A pathologic EEG pattern resembling normal α rhythm, but which is monotonously present despite noxious stimuli.
α Rhythm	A specific spindle-like pattern of EEG activity, containing α band frequencies. This pattern is maximal over the occiput while the eyes are closed but the patient is awake and disappears during arousal or deep sleep.

Analog	A continuously variable parameter, e.g., a voltage.
β Band	A spectral range of frequencies from 13 to 30 Hz.
Common mode	That part of the voltage signal (with respect to a third "ground" site) that appears at both measurement sites. Ideally, subtraction of the voltage at one measurement site from the other will eliminate the common signal.
$CMRO_2$	The cerebral metabolic rate of oxygen. The global (mixed gray and white matter) rate given for awake adult men is approximately 3.5 cc • 100 g^{-1} • min^{-1}.
CSA	Compressed spectral array. A pseudotopographic display of the distribution of power in different frequencies over time.
δ Band	A spectral range of frequencies from 0 to 3 Hz.
Diaschisis	A phenomenon in which injury in one hemisphere causes disruption of the corresponding site in the contralateral hemisphere.
Digital	A measurement that has been quantized into discrete steps and represented as a binary integer.
DSA	Density spectral array. A display of the distribution of power in different frequencies over time using the X-axis for frequency, the Y-axis for time, and dot density for power.
FIRDA	Frontal intermittent rhythmic δ activity. A pathologic EEG pattern frequently seen following ischemic injury.
Impedance	The total resistance to the flow of alternating current. Impedance is the complex sum of ohmic (DC) resistance and the reactance (frequency sensitive resistance).
Montage	The choice of electrodes on the scalp from which to record EEG.
PLEDS	Paroxysmal lateralized epileptiform discharges. A pathologic EEG pattern frequently seen following ischemic injury.
Quasistationary	A signal or measurement that is not truly stationary but changes slowly enough so that adjacent epochs are essentially similar.
Stationary	A mathematical term denoting that statistical description of a signal does not change over time.
Stochastic	A process in which the output can be modeled statistically rather than deterministically.
θ Band	A spectral range of frequencies from 3 to 7 Hz.

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A NEUROSURGICAL PRELUDE TO THE YEAR 2000

Derek A. Bruce, MB, ChB

Our perception of neurosurgery in the next century is per force limited by our current knowledge of the speciality and its history. Twenty years ago the clinical application of computed tomography scanning was not practical and even the use of magnetic resonance imaging (MRI) as a clinical tool for diagnosing central nervous system disease had not been conceived of. Yet these two radiologic techniques have revolutionized the clinical neurosciences. (Whether or not these advances have contributed to improved, long-term survival in the patients whose diseases are identified at a much earlier phase is not clear.) To predict the future of neurosurgery it is necessary to imagine what advances in technology, in fields outside radiology as well as within it, will contribute in the near future to the clinical speciality of neurosurgery. In an effort to foresee the future it is possible to combine solutions to some of our current problems and what advances will be required to make them possible, advances in basic biology, developmental and molecular, that are likely to impact on the speciality, and to imagine what as yet undeveloped technology we would wish for, and thus to produce a painting if not a photograph of neurosurgery in the twenty-first century. It is certain that some areas will be more affected by the coming changes than others, and I focus on these areas in which change is either already occurring or in which advances in research, at a basic level, are poised to have an influence. These areas range from the ethical and societal role of the neurosurgeon, epilepsy therapy, vascular disease, tumor therapy, trauma, and the enhancement of neurologic functioning.

ETHICAL CONCERNS

In the United States and Canada, the ethical and societal demands on the neurosurgeon are different and it is difficult to foresee how the current stress

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in the US health care delivery system will alter the landscape of neurosurgical practice and the expected performance of the neurosurgeon. As the system is financially restrained, there will be limitation of both the development and implementation of new technology. It seems certain that pooling of resources and increased sharing of these technical developments will occur and that complex problems of neurosurgery will be treated in fewer, larger neurosurgical centers. Public policy on such issues as abortion and therefore the use of fetal tissue for neural transplantation will clearly affect future development and should currently be a major topic in neurosurgery meetings and policy making. The public duty of the neuroscientist is the clear discussion of the potential losses or benefits to the society of interfering with such progress without the burden of religious prejudice or subjective bias. The neurosurgeon who treats children is already involved with prenatal diagnosis of a variety of central nervous system (CNS) diseases that require recommendations to or at least discussion with the parents concerning the likely outcome and possible therapy, including abortion. If the society denies the parents any option other than the natural course of the pregnancy there is no point in continuing expensive prenatal studies because there is no decision to be made. A morally easier approach to this problem, one that avoids the difficult and often painful and divisive discussion of abortion, is to consider fetal surgery or gene altering therapy to correct an inborn error of metabolism. This may be another route by which to approach the problem of fetal abnormality, but should not be used as an excuse for the neurosurgical community to avoid playing a role in the greater moral debates. Focusing only on lines of therapy that are ultimately to our own benefit by producing more patients for surgery is a clear conflict of interest that diminishes the importance of any testimony that we may make.

The society as manifest through the health care delivery system is likely to demand increasing proof of the benefit from expensive procedures, e.g., neurosurgical operations, and if such is not forth coming these procedures will be eliminated or at least strictly controlled. It is then one of our tasks to convince the society that individual benefits remain as important within a free society as do national ones, because it is true that if neurosurgery was abolished tomorrow the impact on national health as measured by mortality or morbidity statistics would be unnoticed and the cost savings stand out as the most obvious benefit.

Patients will continue to demand a greater input in the decision-making process and will demand more objective criteria than the surgeons last experience on which to base their decisions. How do the mortality and morbidity figures that are in the current literature apply to individual cases of neurosurgeon, patient, and disease process and therefore what are appropriate figures for a given neurosurgeon to quote to an individual patient? Finally, as a result of increasing knowledge at the molecular level, e.g., the human genome project, increased numbers of rare diseases will become amenable to diagnosis and treatment, even in utero. This will increase the need for widespread cooperation in the collection and treatment of adults and children with rare diseases and should force us to work cooperatively rather than competitively to supply the most logical, sensitive therapies to our patients that have measured long-term effectiveness at the most reasonable cost.

These social, moral, and ethical questions are issues for our speciality as a whole because the neurosurgeon in his or her community implements the neurosurgery. It is this neurosurgeon who is the measure of our speciality and its strength or weakness.

EPILEPSY

The surgical treatment of intractable epilepsy has been limited to a few centers and is essentially unavailable to the many patients who could be helped, predominantly because of the generally poor education of neurologists about the current safety and good results being obtained by surgical therapy. A recent National Institutes of Health sponsored consensus conference concluded that surgery is an acceptable therapy in a select group of seizure patients and that it is underused.[11] Thus, interest from the neurologic community to identify patients who might be surgical candidates has shown an exponential increase. This seems to be especially true in the pediatric population. Current techniques for localization of the epileptogenic focus are based on external electroencephalography, video monitoring, blood flow and metabolic studies with positron-emission tomography or single photon emission tomography scanning and the use of subdural or intracerebral monitoring electrodes. The problems are of localization, both of the epileptogenic cortex and of normal areas of brain function that are at risk for damage by corticectomy or lobectomy. Magnetoelectroencephalography is currently being evaluated as an expensive but possibly superior means of detecting and localizing seizure foci.[3] This technology may also serve to define cortical localization of motor areas, speech centers, and so forth in a noninvasive way. If the current interest in epilepsy surgery continues and the long-term results prove as good as short-term ones, the technology to improve localization will get better and it is likely that invasive monitoring will become a rare necessity. The future role that neurosurgery will play will be dependent on the development of new drugs and further insights into the production of epilepsy.

Localization of both normally and abnormally functioning cortex will improve. Already localization of cortical function has been demonstrated by MRI and it is likely that MRI spectroscopy phosphorous or proton will give further metabolic information that will aid in the process of localization.[2, 10] Positron-emission tomography scanning, while of proven value, is expensive and limited to a few centers. Single photon emission tomography scanning, which is accessible in more centers, will probably develop an isotope that will allow for better metabolic studies to aid in the noninvasive identification of seizure foci. A gene has been identified in animals that appears to be implicated as a source of epileptogenicity. As more information is derived about the molecular function of specific neurons and neural processing, e.g., speech, it is likely that molecular markers can be developed that will identify neurons involved in speech, motor function, and so forth. Thus, it is foreseeable that specific localization of epileptogenic neurons and identification of specific-function neurons will be possible using molecular labeling techniques that could lend themselves to intraoperative localization using such techniques as fluorescence, allowing more exact and safer cortical resection. If such exquisite localization is possible the cellular ablation may be achieved by the use of intravenously administered antibodies or specific cellcidal agents. If such biochemical localization becomes feasible there will be altered anesthesia requirements for drugs that do not affect the transmitter, receptor, and enzymes systems that are to be labeled. It is certain that this will present a major research challenge because already with the use of evoked responses, whether sensory or motor, a consistent level of selected anesthetic agent and temperature stability are required.

ENHANCEMENT OF NEUROLOGIC FUNCTION

The ability of neurologic surgery to enhance human brain function will be a theme of the twenty-first century. The demand of neurosurgery may be that the surgical intervention improve the person's brain function as opposed to relief of pain, improved mobility, or temporary prolongation of life. Already the role for epilepsy surgery, as intervention is performed earlier in development, is to try to prevent the educational losses that have resulted from either poor seizure control or medication effects and thus produce a more functional child. Similarly, surgery to relief spasticity, e.g., selective posterior rhizotomy, is done to improve the functional skills of the child with cerebral palsy. Other such current attempts to improve function are the surgery to implant either adrenal medulla cells or fetal dopaminergic tissue into the human brain.[7] Similar implantation therapy has been suggested for Alzheimer's disease. A further development in this direction is the external delivery of neurotransmitters into local brain areas or the cerebrospinal fluid. Neurosurgery is likely to be called on to develop and test delivery systems for these agents and to be part of clinical trials. As the understanding of brain function increases, and the human genome project identifies the genes responsible for many of the familial patterns of brain dysfunction, e.g., dyslexia, will it be possible to selectively enhance a whole variety of specific neural functional modules by some invasive procedure, thus effecting therapy for deficient brain function ranging from Tourette's syndrome through the major psychiatric diseases to such functional disturbances as dyslexia and learning disability? While it is certain that major brain surgery will not be the answer for these problems it is certainly possible that delivery of the appropriate agents will require the involvement of the specialty.

Increased information about the molecular biology underlying the development of the human brain may allow for the ability to recreate some of these steps and thereby enhance CNS repair after stroke and trauma and may permit modification or manipulation of brain function in utero. What will be the ethics of such interventions both to modify known existing disease and to maximize later brain function by increasing IQ?

Finally, as interaction between computer chips and biological systems develop the biological computer will become a reality and implantable devices will become available to take over lost CNS function.[1, 6] Already devices such as an artificial visual system function over very short time frames. Function in the damaged spinal cord may turn out to be amenable to such implantation as the only means to reinstigate function.

VASCULAR DISEASE

Advances in interventional radiology are revolutionizing the treatment of vascular diseases of the brain. The use of tracking catheters to embolize arteriovenous malformations or occlude major feeding arteries is established as is the usefulness of these catheters in treating arteriovenous shunts, e.g., carotid cavernous fistulae and dural malformations. The use of similar techniques to treat aneurysms of the intracranial vessels is still in its infancy, but undoubtedly will play a major if not the major role in therapy. Balloon angioplasty is now used to treat vascular spasm and may prove beneficial as a means to deliver anticoagulants to treat cerebral emboli and thrombosis. As new radiologic techniques, e.g., MRI angiography, identify smaller aneurysms and occult arteriovenous malformations the results of open surgery for these lesions will be compared directly with the results and costs of transvascular surgery. It seems certain that the pendulum will settle on the side of transvascular surgery for many of these lesions. The technology to guide the catheters will become more sophisticated, possibly by combining some external steering system such as magnetic fields, with stereotaxic coordinates to simplify the access of the catheter to the appropriate vessel, resulting in an automated system. Newer thrombotic agents will increase the safety of producing clotting in the lesion. Once again excitation of a probe on the catheter by the gamma knife or focused magnetic fields will allow more controlled thrombosis without the risk of pulmonary embolization.

Extracranial vascular disease may ultimately be prevented by genetic modification to those individuals without the necessary enzymes to handle blood fat metabolism. As plaques are identified at an earlier stage by imaging techniques, local delivery of medication at the site or modification of free radical release by systemic medication or balloon angioplasty may all prevent development of plaques that are currently best treated by surgery (carotid endarterectomy). Thus, to maintain a role as a member of the team that will be treating lesions of the brain and its blood vessels that currently fall into the operative category it will be necessary for neurosurgeons to be facile with these techniques and to use their knowledge to promote research and further advances in the closed surgical treatment of vascular disease of the brain. As these techniques develop it will be necessary to give increasing numbers of anesthetics outside the standard operating room setting and possibly within a magnetic field. The later currently presenting a problem for the majority of the monitors in use.

The exact role of focused beam radiation therapy in the treatment of vascular lesions of the brain is not yet established. The value of such techniques, e.g., the gamma knife, in the treatment of small deep-seated arteriovenous malformations is clear, although the time to obliteration is 1 to 2 years. Whether these techniques alone or in concert with tracking catheters will be applicable for the treatment of aneurysms is not known but seems likely.

BRAIN TUMORS

The acute phases of treatment of large tumors of the CNS are likely to remain surgical for some time: a tissue diagnosis is required and removal or debulking of the mass is necessary for improvement of neurologic function or indeed may be lifesaving. Similarly, the hydrocephalus that accompanies many brain tumors still requires mechanical diversion. However, as the molecular mechanisms of cell growth are discovered and the perturbations that are present in benign and malignant tumors are understood, it is likely that surgery will become an increasingly less important part of therapy. A cadre of neurosurgeons with knowledge of and direct involvement in molecular biological research are necessary to ensure continued contributions by the neurosurgical community into the treatment of CNS tumors. Once the mechanisms of abnormal rates of cell division are delineated and methods to modulate the genes and enzyme systems within the cell are available, there will still be a problem of how to deliver the treatment to the tumor. The development of delivery systems is likely to be a valuable contribution of the operating neuroscientist.

The use of robotics in the resection of tumors, especially those that are deeply located, will increase because it is easier to be sure that the three-dimensional mass has been resected if one can superimpose the pattern of resection of the tumor on the preoperative tumor image. Advances in three-dimensional imaging have made it possible to create an image of the tumor in three-dimensional space and then program the robot to excise exactly that volume of tissue. The problem with gross tumor resection is to be able to identify the tumor margin from normal brain; by giving the operator exact knowledge of the position in the brain and the exact dimensions of current tumor resection it will be easier to match the resection to the preoperative scan. Studies will be required to demonstrate that the imaging techniques do indeed separate tumor from normal brain. There will certainly be situations in which brain infiltrated with tumor will be identified as tumor on imaging and the neurosurgeon will always be required to decide at what point intraoperatively the resection should stop to prevent damage to functional brain. Current, fully robotic systems are very expensive but as the computer software improves it will be possible to have a computer memory on the operating microscope that will plot the three-dimensional resection as it proceeds and allow for this to be superimposed on the preoperative image, thus informing the surgeon in real time as to the extent of the resection. A computer-connected brain probe is currently available that, after calibration, records in real time the locus of the probe in the brain to allow the surgeon to better gauge his or her position and the extent of any resection.

Another need in current neurosurgery is to identify the tumor from normal brain. As commented on in the section on epilepsy, it will become possible to mark the tumor with biological markers that then will be identified at surgery, helping to define the tumor margins and avoid injury to surrounding brain tissue. Finally, techniques will be developed to insert compounds directly in the tumor bed that will specifically kill the abnormal cells, leading to increased probability of local tumor control. Brain tumors most commonly recur at the initial tumor site and therefore should lend themselves well to this approach to therapy.

Technical developments in the use of split cranial bone, free tissue flaps, fibrin glue, and the combining of various subspecialities has led to a rapid expansion in the amount of surgery being done for lesions that involve the skull base. The advances required here are for better bone substitutes for reconstruction, better methods to repair the basal dura to prevent spinal fluid leakage and infection, and methods to satisfactorily handle the problems of involvement of the cranial nerves and blood vessels that pass through the skull base. Already it is possible to anastomose the intrapetrous carotid artery, making radical resection of tumors in this area more possible. The largest problem is that many of the tumors that occur in this area in young people are histologically benign but locally invasive and, because of the many structures passing through the skull base, wide local margins of resection cannot be obtained. This predisposes to local recurrence, often requiring multiple operations without cure. Once again the ultimate answer for these tumors is to understand the biology and use biochemical means to manipulate the tumor growth. Short of this there will be increased use of focused beam radiation for these lesions and the proton beam, which currently is resulting in lower recurrence rates for tumors like chordoma.

The future for the neurosurgeon as a member of the team treating brain and spinal cord tumors is dependent on involvement in the many interacting disciplines that will ultimately lead to cure for both benign and malignant disease e.g., radiology, molecular biology, tissue transplantation and substitution, radiation biology, computer science, as well as keeping up to date with advances in other surgical specialities, e.g., otolaryngology and plastic surgery.

TRAUMA

The most recent advance in neurosurgery is in the area of trauma prevention and ultimately this is the best possible way to manage trauma in society. It is naive to believe that children and adults will change their behavior so dramatically in the next 20 years that trauma will no longer be a major public health problem. Thus, there will be a role for neurosurgery in the treatment of traumatic injuries to the brain. The purely mechanical lesions are unlikely to be treatable by any means other than surgery, e.g., epidural, large subdural, and intracerebral hematomas. Acute medical therapy to control brain swelling, brain edema, and the secondary effects of release of excitatory neurotransmitters will continue to develop. Monitoring of the intracranial pressure has contributed a lot to our understanding of the cause of death after head injury and treatment of elevated intracranial pressure has been a main stay of therapy. It is clear that often the increased intracranial pressure is only a reflection of disturbed tissue function and what should be treated is the disturbance of biochemical function. The recent research on the deleterious effects of excitatory neurotransmitter releases following seizures, ischemia, and trauma has opened a potential line of therapy designed to directly affect the cause of secondary cellular damage.[5, 9, 12] Compounds that block the activity of these putative neurotransmitters are likely to become a major line of therapy. Increased understanding of the events occurring in the white matter is also likely to result in membrane stabilizing therapy to prevent progressive axonal damage. Thus, specific medical therapy for the treatment of the brain-injured patient will be the treatment of choice for those with diffuse axonal injury, multiple contusions, secondary ischemia, or intractable seizures.

Monitoring of the intracranial pressure will continue to be of use, but is likely to be superseded by more elegant monitoring of cerebral oxygen content, tissue lactate, and possibly local blood flow and metabolic activity, all by noninvasive methods. Such nonsurgical intensive care will be the best approach to selecting therapy and, it is hoped, result in improved functional recovery. More certain methods to determine those patients with irreversible brain damage will allow salvage therapy to be focused on the patient with a chance to recover consciousness.

In the stage of recovery and rehabilitation some of the techniques described previously to enhance neurologic function will be applicable to this group of patients. Will it be possible to modify the brain milieu to promote healing by using growth factors to recreate the developmental environment?[4] Will it be possible to transplant or replace with small biological computers areas of brain and spinal cord loss? This is likely to be a fruitful and beneficial area for neurosurgical research.

PAIN

As the average age of our population increases, there are greater numbers of patients with cancer. As a result of better therapy those patients are surviving longer. This results in many patients with metastatic disease and pain. Increased knowledge about neurotransmitters and their receptors should make pain control easier. As evidence is accumulated suggesting that specific cortical structures are involved in pain perception, neurosurgeons are likely to have a major role in the development of effective central measures for relief of pain and preservation of function.[8]

CONCLUSION

It is clear that there will be changes in the diseases treated by the neurosurgeon and in the types of therapy applied. Many of the purely mechanical diseases, e.g., intervertebral disk disease, spinal fractures, intracerebral hematomas, large brain tumors, hydrocephalus, and so forth, will probably continue to be surgically treated though presumably instrumentation and materials will improve. There will be increased use of stereotaxic procedures to accurately deliver neurotransmitters and transplanted tissue. As a result of the increased application of molecular biological tools both anesthesia and monitoring techniques will change. However, if the goal of the neurosurgeon remains that of understanding brain development and function and being able to surgically treat those diseases that are amenable to such therapy a whole new vista is opening. The surgical neuroscientist should be able to retain a major role in the research and therapy of many CNS diseases and may find an even greater role in the reconstitution of the damaged nervous system. The advances in neurosurgery will demand more sophisticated anesthesia and analeptic sedation plus development in monitoring that will be appropriate for the coming age. These needs plus the increased ability to medically treat diseases such as trauma and stroke in the intensive care unit should serve to tighten the bond between neurosurgery and anesthesia.

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NEUROANESTHESIA

A Look Into the Future

William L. Young, MD

Prologue

Jamais N. Pensepas, Professor and Chair of Clinical Neurobiology (Interventional), led his gaggle of sophomore medical students into the brightly lit procedure room and had them stand up against the unseen barrier that disinfected the sterile area; a soft crackling noise reminded those who had strayed too far into the energy field. J.P. cleared his throat, and with an expansive movement of his arm began to speak, "Today we are going to observe one of the few remaining indications for an open craniotomy—vascular malformation ablation." He continued speaking, now jabbing his finger absentmindedly in the air.

"When I was a medical student, a hundred years ago, transcranial magnetoimmunotherapy had just about eliminated the need to operatively attack tumors. Hell, I was one of the last to be trained by an old-style neurosurgeon under Charlie Stein. Field-driven multiclonal RAES-antibody ablation of all vascular malformations had become commonplace, if less than perfect. Torner and Ward had introduced anti-ischemic oncogene induction. If Fitzkliot hadn't perfected neural bridging, we might have all forgotten how to open the damn skull.

"Then, the Re-ans, our colleagues in Reanimatology, who used to be called *anesthesiologists*, perfected the fullerene-based vectored heat transfer methods, which are the noninvasive techniques of cooling and rewarming. What amounts to souped-up antifreeze is introduced into the systemic circulation and then bombarded in a Jenoh hyperionization field. The stuff is given intravenously,

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the way many drugs were routinely given before the advent of transmucosal and dermal focusing methods. Using optical transthoracic cardiac innervation they can start and stop the circulation on a dime. The development of these techniques gave us the perfect opportunity to definitively treat larger arteriovenous malformations and some stubborn cerebral aneurysms.

"When the patient arrives here, the Re-ans transfix consciousness with one of their oldest drugfocus tricks; the newer ones interfere with our steering field. They place the patient in a layered Yitzakian matrix using one of the new five H convex magnetoids and adjust the field so it deforms ever so slightly the CNS *Jaune* receptors. While the patient breathes Tri-ox, they slip in a nebulized mixture of various poisons that only interact with those deformed receptors that are in the field. The result is a tranquil, analgesic patient.

"We expose the cortical surface and use resonance angiography with angular convergence to construct an exact model of the dynamic vascular anatomy, right down to the normal capillaries at some distance from the margin of the nidus. Next, the Re-ans pass off a series of autoemission positronic scanners that are placed on the cortical surface and can reconstruct in three dimensions full metabolic and hemodynamic profiles of all surrounding tissues on one of these 'head's up' displays visible in the corners."

The students squinted at three-dimensional images of what appeared to be a brain hovering in each corner of the room. The virtual images seemed to hang in mid-air, slowly rotating, stopping, and then reversing direction. Adjacent to each image, series of alphanumeric characters and various waveforms of different colors streamed into the middle distance and disappeared. Various brain areas were seen to light up with different colors, each pattern remaining for a few seconds and then being replaced by a new one.

J.P. continued, "After getting baseline information and correcting for background positronic density, the circulation is stopped. We cannulate a draining vein and then inject the ablation material, which is also fullerene-based, in a retrograde fashion. Do you smell that sweet smell?"

Numerous noses went up and began sniffing.

"It's the yellow stuff on the table there. We call it a 'buckyball banana daiquiri.' Using the magnetoid steering field, we form it into the exact shape of the malformation while the Re-ans monitor *hypothesized* cellular function in the normal tissue contiguous with the malformation. We say *hypothesized* because there is no circulation and the patient's cold during all this. The computer takes into account all of the available physiologic and anatomic information. This helps us determine the progress of the fullerene ablation so we don't bag any branches supplying functional tissue or simply overstuff the thing.

"When the nidus is filled and the 'banana daq' has been fixed by tweaking the magnetoid field, the malformation is no longer a risk to the patient. The Re-ans jump-start the circulation and check cellular function just to make sure that the computer didn't hypothesize the patient's piano lessons into never-never land, and that's it. Mission accomplished.

"The whole procedure takes about 30 minutes. The patients go home the same day with homeostasis monitors placed behind an ear and the Re-ans monitor neural and systemic processes for about a week. You know, as soon as they can figure out how to monitor cellular function in that steering field through the intact skull we may not even have to open the head."

He looked deadly serious for a moment and said in a low voice, "Some of us hope they never do . . ."

I

> The White Rabbit put on his spectacles. "Where shall I begin, please your Majesty?" he asked. "Begin at the beginning," the King said, very gravely, "and go on till you come to the end: then stop."
>
> LEWIS CARROLL

Where is anesthesiology headed in the coming years? Will we still *call* ourselves anesthesiologists 100 years hence? And will neuroanesthesia continue to develop as a subspecialty? This essay is *not* meant to preview imminent breakthroughs that will magically transform our practice. Instead, we examine the question of focus and general direction for future progress.

Anesthesiology matured as a specialty during the middle years of this century and enabled operative neurosurgery to undergo a startling change of scope. With the ability to anesthetize older and sicker patients in longer procedures using more creative positioning, the very notion of what was possible had to be redefined. A new paradigm* for treatment of central nervous system (CNS) disease had arrived.[34] Are we poised at the brink of yet another paradigm (Fig. 1)? Can we further develop the expertise to assess neural function and intervene as it relates to the care we provide patients?

In the past 50 years we have made astounding gains in the care of the neurologically injured patient. Murtagh and Smith[46] reminisce:

> For the patient with acute life-threatening intracranial hypertension, usually as the result of trauma, although sometimes a tumor, acute hydrocephalus, or hemorrhage, and lacking any indication to the problem, the approach would be to take the patient to the operating room and make a series of burrholes to find an epidural or subdural hematoma. If these were not found, the brain would then be probed with a metal cannula, in the hopes of detecting an intracranial cyst, clot, or solid mass that could be removed. . . . Lacking success with any of these endeavors, the next step was to do an external decompression by making a large scalp flap, removing a large bone flap and opening the dura. Under these circumstances, the traumatized or pathologic brains in these hypoventilated, hypertensive patients would literally explode through the resulting opening and large portions of the brain itself would have to be removed. Not infrequently in the case of trauma, decompression would be done bilaterally. If the patient survived, he was neurologically devastated, and had what was known as a 'bucket handle' head, i.e., bilateral depressions with a small ridge of bone down the vertex.

The stage was set for the first neuroanesthetist's entry onto the scene. General advances in anesthetic practice could begin to offer the neurosurgical patient significant improvement in the chances for a functional outcome.

A seminal group of practitioners realized that there were unique problems

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*Kuhn[34] writes, ". . . like an accepted judicial decision in the common law, [a scientific paradigm] is an object for further articulation and specification under new or more stringent conditions." In this sense I will use paradigm to imply a collective perception of the current management means and goals for a medical speciality. Just as it would be impossible to discuss relativity theory in terms of Newtonian physics, before the advent of modern anesthetic techniques, modern microvascular neurosurgery would not have been conceptually possible.

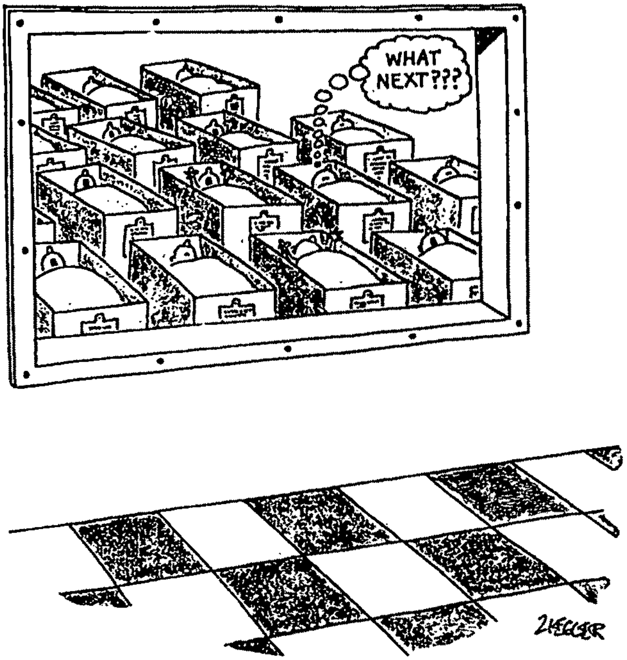

Figure 1. What next? (From Ziegler: "What Next???" cartoon. The New Yorker April 21:33, 1980; with permission.)

relevant to the neurosurgical patient. Those interested in this fledgling trade-in-craft began clinical and laboratory research, overlapping certain areas traditionally viewed as the domain of other specialties. Michenfelder[44] highlighted three areas in which neuroanesthesia has made important contributions to clinical neuroscience†:(1) effect of anesthetic agents on cerebral blood flow (CBF), cerebral metabolism, and intracranial pressure (ICP), (2) cerebral protection/resuscitation,‡ and (3) the pathophysiology and management of venous air embolism.

But Michenfelder argues that, despite our successes, we have somehow gotten off track through the devices of "pseudoacademicians." His case in point was the lightening-rod editorial[25] condemning inhaled anesthetics in the neurosurgical patient. He writes:

> But the die was cast. Never mind that halothane had been the most commonly used anesthetic in neurosurgery for almost 10 years the world around at that time. Never mind that up to that time no neurosurgeon had made known his suspicions that halothane caused a tight brain. Never

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†I use the term *clinical neuroscience* to denote every -ology and -surgery that deals with the clinical management of CNS disorders. This includes not only medical and surgical management, but also clinical brain imaging and related basic science efforts in the realm of neural function.

‡Documenting the cerebral effects of cardiopulmonary resuscitation deserve inclusion here.[57]

> mind that at the Mayo Clinic alone we had anesthetized more than 2000 patients undergoing craniotomy using halothane, and neither anesthetist nor surgeon ever recognized an intracranial pressure problem. Certainly the latter group, *i.e.*, the neurosurgeons, are not noted for their reluctance to identify such problems.

Crosby and Todd[16] pick up this theme in a more recent editorial:

> There is perhaps nothing more fundamental to the practice of neuroanesthesia than the assumption that any increase in intracranial pressure (ICP) is potentially deleterious and, hence, is undesirable, particularly in patients with mass lesions. . . . Some might, in fact, argue that the primary task of the neuroanesthesiologist is to conduct an anesthetic in such a way that there is no possibility for an increase in ICP. . . .

Crosby and Todd proceed to take a "relativistic" view of ICP, citing numerous cogent examples where absolute levels of high ICP do not affect patient survival or well-being. Matsumura and Cole[42] rebut this approach a few pages later taking an "absolutist" position:

> A perspective that views volatile anesthetics as safe because the brain does not herniate or the perfusion pressure is adequate, has missed important aspects of neuroanesthesia. Increases in [brain volume] can reduce surgical exposure, worsen retractor injury, or result in critical reductions in local perfusion pressure that are not detected by standard 'global' monitoring.

How do we reconcile these views? Are we fixated on ICP control?§ We have progressed from the bucket handle head[46] to an environment of awesome anatomic and physiologic trespass that enables marathon neurosurgery and produces functional survivors therefrom. There is no doubt that the dragon of runaway increases in cerebral blood volume, in the original incarnation, has long been slain. Notwithstanding, we tend to devote an inordinate amount of academic time and intellectual energy to the subject of ICP divorced from any meaningful correlation with clinical outcome. It tends to act as a lens through which we see our "mission" in the operating room. It is not uncommon to ask a resident during the middle of a neurosurgical case why we are hyperventilating the patient *after* the skull is open and to receive an answer like "to prevent increases in ICP" in reply.

A key point Matsumura and Cole[42] touch on is that we cannot assess what our anesthetics do to cerebral function and autoregulation because we do not have the tools to look for adverse effects (or any effects at all, for that matter). Crosby and Todd[16] began their piece with the exhortation from Pickering: "Not everything that counts can be counted, and not everything that can be counted, counts." There is no arguing the latter point. But what about things that count that cannot be counted? Should we consider the possibility that we are missing something?

Over 20 years ago Wollman wrote an editorial attempting to put into perspective a number of novel terms and concepts that had come bursting forth into the clinical arena. It was a violent lurch forward with terminology such as *vasomotor paralysis, luxury perfusion, intracerebral steal, inverse steal,* and *Robin Hood syndrome.* He writes[68]

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§This is not to say that all obsessions are counterproductive. "I am obsessed," Woody Allen says, "by the fact that my mother genuinely resembles Groucho Marx."

> Do these interesting situations occur in patients? Yes! Can we guess which syndrome will occur in whom? No! . . . Let us accept the basic phenomena, the picturesque names, and the variability among patients. We must then ask—what is a practical clinical approach to the patient with regional cerebral vascular problems? We hope that those who treat such problems will soon be equipped to measure [regional cerebral blood flow], and will do so before, during and after a proposed therapy or anesthetic. . . . The know-how and the means of paying for their use must be developed.

Goethe quipped, "You see what you look for, you look for what you know." We *may* know what to look for, but the salient and sad point is that one of the few organ systems we do not routinely monitor is the CNS. Not only is the CNS the site of action for most of our drugs, it is also the operative target. Today, the only routinely available means of assessing the CNS impact of our clinical management is electroencephalogram (EEG) or evoked potentials, and, as anticlimactic as it may seem, to either wake up or never anesthetize the patient to begin with. Despite the cascade of both computerized EEG machines and publications concerning their use since the early 1980s, controversy dogs EEG monitoring and it remains just out of reach for not only the average practitioner but also for many neuroanesthetists.

Most of the concepts that Wollman[68] seemed to be so excited about in his editorial remain either laboratory curiosities or relatively ignored. For example, consider *cerebral steal.*[1] The concept of *cerebral steal* has always been controversial. The colorful imagery belies the physiologic principles involved (see Wade and Hachinski[65]). It took more than 10 years after steal was demonstrated[27] for investigators to show that a *drug* could redistribute CBF to ischemic areas[8] (and not because barbiturates are anesthetics, per se, but rather because they may be cerebral protective agents). Then it took another 10 years for Warner *et al*[67] to investigate the phenomena of steal for inhaled anesthetics in a rat focal ischemia model. Because the emphasis in neuroanesthesia research has been to define ICP and related perfusion effects of anesthetic agents, it is anybody's guess when we will be able to assess regional cerebral treatment effects in humans in the operating room and intensive care unit.

II

> A curious game in which a very small ball is placed in a very small hole
> with instruments ill-suited for the purpose. . . .
>
> WINSTON CHURCHILL, ON GOLF

Regarding goals for the future, a pertinent question is how to define neuroanesthesia. This is not as trivial as it might seem. What begins as descriptive, all too often evolves into something prescriptive. For example, *descriptive* analyses of innovative music becomes *prescriptive* (i.e., rules not to be broken) for newer generations of composers.

First, who are neuroanesthesiologists? The now 20-year-old Society for Neurosurgical Anesthesia and Critical Care is one means of characterizing the group. From 1972 until 1989 the number of anesthesiology training programs with a dedicated division or section on neuroanesthesia with residency or fellow training increased from 6 to 64,[2] but the number of people who identify themselves with (or are willing to pay the dues for) the society has remained relatively constant at about 500 over the past several years (Smith DS, personal communication), a figure that includes a number of neurosurgeons and other clinical scientists as well. It does not appear likely that there is going to be any increase in our numbers in the near future, unlike more "numerically" practical interests such as cardiac or obstetric anesthesia or emerging subspeciality interests such as ambulatory or pain. We are destined, at least in the short run, to be primarily creatures of academic, referral-oriented centers. Many, if not most of us, remain involved to varying degrees with anesthetic care of all types. In the present state of the art, a practice *absolutely* confined to neurosurgical procedures is neither practical nor, I would venture to guess, desirable. At any rate, it is not the norm.

In addition to possessing the formidable skills required of a modern anesthesiologist, is a neuroanesthesiologist going to be defined as someone who merely controls ICP and is an expert in the diagnosis and in the detection and treatment of venous air embolism intraoperatively? Although these are no mean feats, one can make the argument that we should broaden our perspective. Maybe *neuroanesthesia* is not so much to be defined by how many hours we log in the cockpit, but rather as an *approach* to a set of peculiar clinical challenges.

Knill[33] recently invoked H.K. Beecher's maxim (see Rothman[55] for a fascinating account of Beecher's contributions to modern bioethics) about the three goals of anesthetic-related research (facilitation of surgical therapy, assurance of patient safety, and provision of patient comfort) to make the case for pursuing anesthetic research into nontraditional areas. He argues that although the incidence of *intraoperative* myocardial infarction has fallen, it remains a *postoperative* problem. Indeed, it is a problem several days after the surgery, at a time when anesthesia is far removed from the case. Why have we made progress in the immediate operative period while not in the early postoperative course? Knill writes[33]

> The explanation for the relative scarcity of investigation into certain hazards of the postoperative period probably lies with the traditional academic orientations of various specialty groups. Surgeons, who have studied postoperative complications, have usually concentrated on those that are readily recognized as directly linked to the surgical procedure itself such as wound complications, shock, and infection, and have tended to ignore those that seemed either anatomically remote from the procedure or partly 'medical' in origin, such as myocardial infarction. . . . Anaesthetists, for the most part, have focused on those problems that arise in the immediate peri-anaesthetic period and have overlooked those that develop afterwards, even though the latter are sometime attributed, rather loosely, to 'the anaesthetic.' Physicians have usually regarded postoperative hazards as 'surgical' or 'anaesthetic' in nature and have almost completely ignored them in their academic pursuits. The serious study of several important problems of the postoperative period would appear to have fallen as a result through cracks in the academe.

The "watershed" zones between recognized lines of medical specialities often can be overlooked. No matter how important the questions or problems might be, they may get swallowed up in the cracks.

This has great relevance for our future direction. The old paradigm that anesthesia was something relegated to medical students or "whoever happened by" is now in the distant past. We are firmly established in the laboratory in many areas related to cerebral physiology. Continuing development as a subspeciality in natural directions, we are poised to expand the horizons of clinical investigation and CNS monitoring in several unique ways, inside and out of the operating room.

Anesthesiologists have made some of the most significant contributions to critical care medicine, but in terms of actual patient care responsibilities, our involvement has been mostly on the general surgical side of the street. There are many fewer settings where anesthesiologists directly participate in neurointensive care. The reasons for this are complex and multifactorial, as the politics, sensitivities, and exigencies of busy clinical practices make it difficult to cross the traditional boundaries of medical specialties.

Still there remain many instances where anesthesiologists' skills can further contribute to patient care. It is not a question of taking over "turf" presently viewed as belonging to other specialities, rather, it concerns addressing problems that otherwise may simply go unattended.

Use of significant hypothermia for brain protection during cardiac surgery is now time honored. Although lesser degrees of hypothermia for both brain[15] and spinal cord[4] protection have been suggested for years,‖ mild hypothermia was never systematically investigated, probably because of the dogma that the protective effect of hypothermia was proportional to the degree of metabolic suppression.

Interest is resurfacing with new evidence that mild hypothermia may be both protective[10] and therapeutic.[28] The cracks in the long-standing wall equating metabolic suppression with protection are widening.[11, 67] Sano et al[56] have recently presented preliminary data that, while isoflurane and halothane are not cerebroprotective in equi-MAC concentrations at normothermia, lowering the temperature by merely three degrees in halothane-anesthetized animals *is* cerebroprotective. This sort of work can inspire us to move away from studying "anesthesia" drug effects and focus on other, perhaps more productive, pursuits.[68]

Yet there is a considerable distance to go regarding introduction of modest hypothermia into the operating room and intensive care unit. Many clinicians aggressively warm patients who might otherwise benefit from a mild hypothermia; and acutely brain-injured patients who spike a fever are likely to have a formal sepsis work-up with temperature left uncontrolled. It is incumbent on us to institute clinical trials and to extend work done on the basic physiology of small reductions in temperature.[59] Otherwise, we will be "wandering in therapeutic circles."[21] Even if it is not possible to demonstrate statistically improved outcome, it would be sufficient at the outset to document that mild hypothermia does no harm.

The adverse impact of elevated plasma glucose[36] on cerebral ischemia is another example of an important idea getting lost in the cracks because it does not fit nicely into the intellectual domain of any established specialty interest. "Medical" by nature, it has a direct bearing on surgical patients, especially cardiac and neurosurgical. Awareness appears to be rising among anesthesiologists, but, with certain exceptions,[35] the surgical literature is practically devoid of the interaction of glucose and clinical brain injury.

‖ In Wollman's cited editorial,[68] his closing remark was prescient, if unheeded: "While we work toward clinical application of rCBF measurements, the interim solution is—cool it!"

III

> I have often recalled a favorite fable of my childhood, a fable about a group of mice who found their community victimized by a stealthy cat. . . . the mice held a sort of town meeting to discuss the problem. One of their number brightly suggested that all they had to do to prevent the cat from sneaking up on them was to have it wear a bell around its neck. As the mice rejoiced over this simple solution, one of their wise elders rose to ask the devastating question: 'But who will bell the cat?'
>
> PATRICIA SPAIN WARD[66]¶

Hypotension, hypertension, hypercarbia, hypovolemia, hypoxia, and hyperthermia—these are all in our realm of control. But at present we can only assess their systemic manifestations. Should we not develop the means to directly assess the end-organ results of these deranged states in order to make more meaningful interventions?

Should we try and bell the cat?

A promising avenue for neuroanesthesia is increased involvement in dynamic imaging of the CNS. *Dynamic* has two meanings: First, *dynamic* in the sense of continuous monitoring (something to which we, as anesthesiologists, are all accustomed) and second, application of these techniques with *dynamic* manipulation of either systemic or cerebral functions. As the distinction between neurosurgical and interventional neuroadiologic techniques blurs, we will find increasing partnership with the radiologist, who will require assistance with blood pressure and pharmacologic manipulation in intracranial catheterization procedures.[50]

Although we are beginning to see experimental progress with induced hypertension to treat cerebral ischemia,[19] a vexing problem for clinical application is that there is no way to monitor, on-line, a *cerebrovascular* correlate of its progress. Indeed, blood pressure management of all stroke patients is much closer to art than science. In the future, thrombolysis of stroke[9] could develop to the point where anesthesiologists will be called on to manage and monitor systemic hemodynamics before, during, and after intervention.[70] First, induced hypertension with cardiac and cerebral monitoring would bridge the period until thrombolysis is started. After thrombolysis, the blood pressure could be lowered until the blood–brain barrier stabilizes. Finally, one could monitor for the development of delayed hypoperfusion, and again use deliberate hypertension if it develops.

Further development of monitoring includes more cooperation between the clinical electrophysiologist for EEG and evoked potential development (the latter is increasingly important, with accelerating interest in magnetic evoked techniques to assess motor function).[37, 60] But we also need to develop the techniques of monitoring parameters that we have taken for granted are *not* available to us. Continuous assessment of CBF, cerebral blood volume, cerebral metabolic rate, and receptor occupancy are examples. Single photon emission tomography and positron emission tomography technology is advancing rapidly, and many of these techniques can be adopted for use in the operating room and intensive care unit to define pathophysiology and avert disastrous outcome. Transcranial[47] and novel Doppler ultrasound methodology,[51] laser Doppler,[13] thermal clearance,[13] and cerebral oximetry[43] are ways of assessing perfusion that have received scant attention to date. Spectroscopy,[39] both magnetic and optical, may find direct applications, and along with other available methods of assessing hemodynamics,[24] can be used to validate novel approaches. With all our writing and talking about increased ICP, we have only recently begun to devise practical methods[38] to monitor for its occurrence in or out of the operating room and have simply relied on technology that has been passed over to us from our surgical colleagues. Even simple elegant concepts, such as measuring brain retractor pressure,[3, 26] have fallen out of view. The initial commercial incarnation of this device was cumbersome and it is no wonder that the neurosurgeons abandoned the idea. A common complaint is that brain retractor pressure monitoring is technologically not feasible. Not feasible? You can be assured that if it were a similar technological problem for rock guitar or keyboard players it would have been solved long ago. The musical instrument digital interface, which allows electronic instruments to communicate with one another, is lightyears ahead of any standard for biomedical equipment to share information.

¶The anecdote was retold by Klawans.[31]

When computer graphics on MTV or Saturday morning cartoons far outstrip the sophistication used for intraoperative monitoring, should we be concerned? In the recent film, "Hunt for Red October," a nuclear submarine is tracked by sonar half-way around the world at 20,000 leagues—and we cannot build a brain retractor that tells the operator how much force is being applied to the brain or gives us an indication of the physiologic sequelae from its placement? Final refrains in this argument are of the "it costs too much" and "what do we do with the information" variety. We will return to this later.

On an ironic note, interest in monitoring the brain is diffusing out of our niche into cardiac anesthesia.[45, 49] It appears that one of the major movements in the recently declared "Decade of the Brain"[22] as regards anesthesiology will be an increasing interest in the cerebral physiologic effects of, and neuropsychiatric outcome from, cardiopulmonary bypass. Will the keepers of the "cerebral flame" ultimately turn out to be our cardiac colleagues?

IV

> Disney, of course, has the best casting. If he doesn't like an actor, he rips him up.
>
> ALFRED HITCHCOCK

There will always be some of our colleagues, Canute-like on the beach, ready to turn back the tide of progress. As Murtagh further recounts[46]:

> While still a general surgical resident, I helped prepare a brain tumor patient for a craniotomy to be done by a visiting neurosurgeon. We had the patient well controlled using an endotracheal tube and general anesthesia and ready for the operation. When the surgeon arrived, he refused to operate on the patient 'with that hose in this throat!' . . . We extubated the patient and maintained him on intravenous thiopental. The surgeon opened the skull and the high intracranial pressure popped the meningioma out like a ball bobbing up in a pond.

The attitude toward monitoring taken by some of our surgical colleagues frequently is sufficiently apathetic to derail the most ambitious and well-meaning clinician-scientist. A typical example would be a craniotomy, with or without intraoperative calamity, after which the patient awakens with a dense hemiplegia. Engaging the surgeon afterward about how one could have monitored for this grim occurrence with the hope of intervening, the uffish# reply is, "There was nothing anyone could have done"—a tolerance born of low expectations.

But recent cries for more outcome studies[30, 41] provide grist for the pundit's mill. How can we assess monitoring and therapy with such a low incidence of intraoperative stroke?[69] We need to look in the right places. An important step forward will be forging alliances with neuropsychologists to enable us to detect outcome differences that are much more subtle than frank stroke.[45, 49]

Of course, there are those who might argue that involvement in areas such as CNS imaging and postoperative care is not our purview, as there are already well-defined specialties to deal with all of this, and that increased and complex cooperation between established medical specialties is fraught with practical and political difficulties. Do we not have radiologists and nuclear medicine specialists to image the brain? Neurologists, psychiatrists and neuropsychologists to occupy themselves with assessment of cognitive dysfunction? Electrophysiologists to monitor EEG and evoked responses? Notwithstanding, as we "saturate" our current paradigm we will be required in the future to increasingly forge interdisciplinary collaborations with other specialists to make true progress.

Collaboration may be a sine qua non for future progress, but financial concerns could well be the rate-limiting step. Who "bankrolls" progress? Should it be industry, government, or the investigators themselves? Falling incomes for clinical departments, coupled with increased scrutiny regarding how much we spend for patient well-being and who profits therefrom,[48] are going to present a significant challenge for progress. Thrown in on top of this will be increasing hurdles for both animal[64] and perhaps clinical research.[55]

In light of such concerns, how do we justify more aggressive clinical study of the brain? Gravenstein[23] has summarized some of the real and hidden costs associated with invasive monitoring, primarily cardiovascular and respiratory. Even though there are studies that claim to justify use of this or that monitor, data are hard to come by in real terms. Although analyses of closed claims can be enlightening, they are biased toward adverse events.[12] More importantly, as Keats[30] argues in his essay on anesthesia mortality, retrospective determination of causes of mortality are based on *judgments,* indeed, frequently from another practice paradigm. His example was a fatal course of ventricular fibrillation after succinylcholine had been given to a traumatized patient. At the time (1958), this was ascribed to hypoxia secondary to use of 80% N_2O. Today, the "correct" answer would be succinylcholine-induced hyperkalemia. His essay examines the interplay of technology and anesthetic mortality, cautioning against implementing monitoring without full study of relative risk-to-benefit ratio[30]:

> Why [is it] we cannot wait for reasonable answers before going off half-cocked, full-steam-ahead to fight dragons and cure problems not known to exist?

Because monitoring the CNS is in such a primitive state compared with other vital systems, Keats' call for caution is worth bearing in mind in the development and implementation of CNS monitoring. But it is hardly "half-

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#Lewis Carroll defined *uffish* as "a state of mind when the voice is gruffish, the manner roughish, and the temper huffish."

cocked" to want to monitor for devastating complications from neurosurgical procedures. When an otherwise healthy 38-year-old mother of three small children has a large arteriovenous malformation resected for control of intractable seizures and then is put into a chronic vegetative state from postoperative brain swelling, this certainly should qualify as a "dragon" worthy of our attentions, no matter how infrequently it might occur.[71] How should we approach the issue of risk and benefit?

A conceptual approach to developing CNS monitoring is the so-called "learned hand rule."[58] In 1947 Judge Learned Hand formulated an explicit, if idealistic, definition of negligence. He stated that negligence occurs if the cost of preventing a mishap (C) is less than the probability that it will occur (P) multiplied by the loss suffered when it does occur (L). Or, recasting this symbolically, negligence (N) may be defined as

$$\text{If } C < P \times L, \text{ then } N$$

Of course it is going to be exceedingly difficult to determine by clinical studies whether we actually prevent any given set of mishaps. However, I believe that we all need to reevaluate our motivations for development of CNS monitoring techniques based on the spirit, if not the literal interpretation, of this concept. The cost of caring for a single symptomatic postoperative stroke is astronomical, both in direct medical care costs and in terms of lost income from the stricken patient.

Demonstrating the financial advantages of preventing perioperative cerebral dysfunction will not settle this issue. As a loosely analogous situation, the staggering amount of money that goes into unnecessary preoperative testing demonstrates how we in the medical community are slow to change longstanding dogmas in patient care. In spite of the cogent arguments against unneeded testing,[53] we merrily continue to order tests and will probably only desist when third-party payers refuse to reimburse for them.

The first step is to carefully examine the cost to benefit ratio of *not* monitoring for neurologic morbidity. With such analysis we can at the very least, as Keats put it,[29] examine events that ". . . can lead to patterns of adverse occurrences not fitting our established taxonomy of errors." This goes not only for neurosurgery but operative procedures of every type, be it cardiac, geriatric, and so forth, where the prospect of cerebral injury is of concern. In spite of the seemingly low incidence of problems, this author believes that, simply on a financial basis, there is ample reason to more aggressively develop our ability to monitor with intent to intervene.

The interests and efforts of neuroanesthesiologists with regard to cerebral injury should be placed into a larger perspective in terms of the practice of medicine and its perception by society. Despite the obvious importance of CNS dysfunction, there is a historic bias toward the "inevitability" of stroke, as discussed in the recent editorial entitled "Nihilism and Stroke Therapy" by Biller and Love[7]:

> To trace the roots of nihilistic attitudes toward stroke, one must begin by analyzing the definition of apoplexy or stroke. Apoplexy means "struck with violence" in Greek and "being thunderstruck" in Latin. Stroke was not seen as an affliction from within the body, but the results of a force from outside the body, perhaps even celestial. This view is reflected best by the definition of stroke in the 1599 *Oxford English Dictionary* as a "stroke of God's hands." The logical deduction was that if the disease were caused by divine intervention, no human intervention such as drug therapy could

> possibly alter the outcome. Often stroke has been referred to as a "cerebrovascular accident," a term that supports the concept of stroke as a random, unpreventable catastrophe. The term "cerebrovascular accident" should be banished from our vocabulary.

Choi[14] has recently pointed out that this "inevitability" factor concerning cerebral ischemia has persisted up until the present at a mechanistic level. Cerebral ischemic damage has been conceived of until recently as a static phenomena that results when demand outstrips supply in the neuropil. It is only recently that we have come to view the process as an *active* one, in which we can intervene with receptor manipulation. This revolutionary concept remains in its infant stage.

Although stroke and cerebrovascular disease continue to be a leading cause of death and disability in many countries, there is no unified "front" for representation of the various facets of clinical neuroscience. We are all familiar with the American Heart Association (AHA) and the American Cancer Society (ACS), but what about the brain? With the recent inauguration of the "Decade of the Brain"[22] there is renewed interest in an "American Brain Association." Rhoton[52] discussed this in his 1990 address to the American Association of Neurologic Surgeons:

> The American Brain Association would bring lay leaders and neurologists, neuroscientists, and neurosurgeons into activities involving patients, physicians, hospitals, medical schools, and research facilities from communities across the nation. It would mount a national fund-raising drive. It would provide funds for equipment in hospitals, educational programs for patients and physicians, and research and training grants. . . . The public has never had an opportunity to contribute to a national philanthropic organization for the brain that has the breadth of activities seen with the AHA and the ACS.

One would assume that we fit under the rubric "neuroscientists." There should be no doubt that we stand ready on the playing field and should involve ourselves in this political arena.

V

Neuroanesthesia will undoubtedly benefit from specific and general applications of new agents and drug delivery systems. "Drug focusing," a concept that Stanley[62] has recently reviewed, will profoundly affect care of the brain-injured patient. One of the major challenges in anesthetizing the neurosurgical patient is terminating the anesthetic precisely at the same time as the surgical procedure, thus enabling rapid differentiation of drug residua from operative trauma. All manner of new approaches beckon, such as novel manipulation of CNS receptors with an array of specific ligands, perhaps clothed in a liposome or some other substance to render them inactive until arrival at the desired time and place. In addition, various kinds of energy fields can be used to influence the interaction of drugs and their intended receptors, including physical activation of receptor sites and modulation of neurotransmitters (or false neurotransmitters). Particularly exciting, and much closer to realization, is a blurring of the distinction between "anesthesia" and direct manipulation of the central adrenergic system.[18]

It is perhaps disappointing that most of our current anesthetic agents have not been demonstrated, per se, to be cerebroprotective. It is hard to swallow, but the choice of anesthetic agent probably just does not matter, analogous to the lack of influence of anesthetic choice on cardiac outcome.[61] Nevertheless, classes of receptor agonists/antagonists involving the *N*-methyl-D-aspartate or more recently described receptor classifications might also effectively straddle the line between "anesthetic" and "neuroprotective" (Warner DS, personal communication).

As the dogma of irreversible injury begins to crumble, a new paradigm approaches the practice of neurosurgery as well. Not only are there fetal and autologous transplants to consider,[20] but recent work portends direct repair of neural tissue. Kliot writes[32]

> An unfortunate result of biologic evolution is a diminishing capacity of the nervous system to recover from severe injury whether it results from a disease process or trauma. Thus, although the central nervous system of lower vertebrates . . . displays remarkable regenerative abilities, the central nervous system of mammals, including humans, is capable of far less spontaneous repair. A tragic clinical example is the patient who has suffered "irreversible" damage to the spinal cord. A major premise [here] is that the term irreversible must be reexamined in light of a rapidly expanding body of experimental evidence. A consensus is clearly emerging that the mammalian central nervous system is host to a wide array of biologic mechanisms that can significantly contribute to the restoration of anatomic connections and physiologic function following injury.

Neurosurgeons heretofore have been primarily concerned with separating the patient from the disease, whereas in the future they are probably going to spend more time putting things in, rather than taking them out (Fig. 2). This will probably occur with the ever-accelerating aid of sophisticated imaging devices such as computerized stereotaxic systems, with the assistance of other surgical specialists[54] and in increasing competition with the radiotherapist[40] and radiologist.[6]

VI

There is no question that clinical neuroscience, in general, and neuroanesthesia, specifically, needs to clarify the fundamental molecular and cellular processes that cause cerebral injury and develop specific treatments to salvage or protect injured tissue.[17] Michenfelder[44] argues that up till the present, we have been phenomenologists, occupied with the *whats* of the problems and not the *whys*. This is true enough. We need to train and support clinicians who have been trained as competent, contributing molecular biologists.

At the same time, two vital directions for advances in the practice of neuroanesthesia are evident. One is to use our abilities as acute-care oriented physicians to help introduce newer approaches to the extraoperative management of the neurologically damaged patient. The second is to improve our means of assessing the CNS effects of our agents and other therapeutic maneuvers. Although we should be curious as to "what's under the hood" and how it works, we have to see where we are driving the bus. Put another way, we need to continue to search for magic bullets, but we still have to know when to shoot.

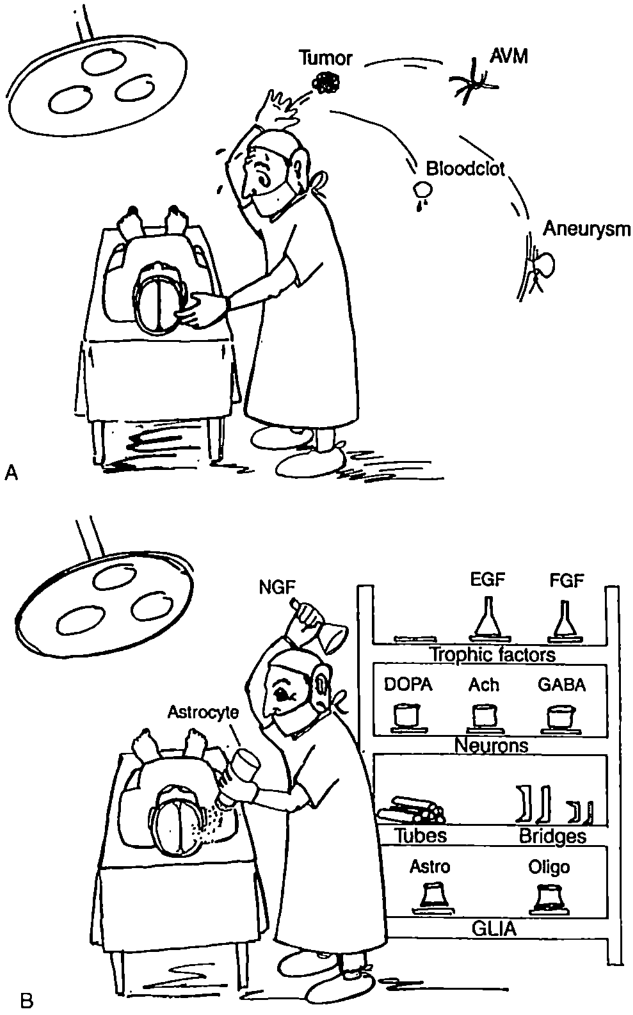

Figure 2. The surgeon of the future will probably spend less time taking things out *(A)* and more time putting things in *(B)*. (*From* Kliot M, Smith GM, Siegal J, et al: Reconstructive neurosurgery: Novel strategies promoting the regeneration of injured dorsal root sensory fibers into the adult mammalian spinal cord. *In* Holzman R (ed): Surgery of the Spinal Cord: Potential for Regeneration and Recovery. New York, Springer-Verlag, 1992, pp 37–52, with permission.)

These efforts are by no means limited to full-time academics. To the contrary, Altman[5] recently emphasized the importance of medical discoveries made by practicing clinicians. He uses the example of the pediatrician who noted increased bleeding among children chewing aspirin gum and suggested that aspirin might be safer than dicoumeral in myocardial infarction. As an outgrowth of this observation, antiplatelet agents have had an enormous impact on the management of both the cerebral and cardiac arteriopath.

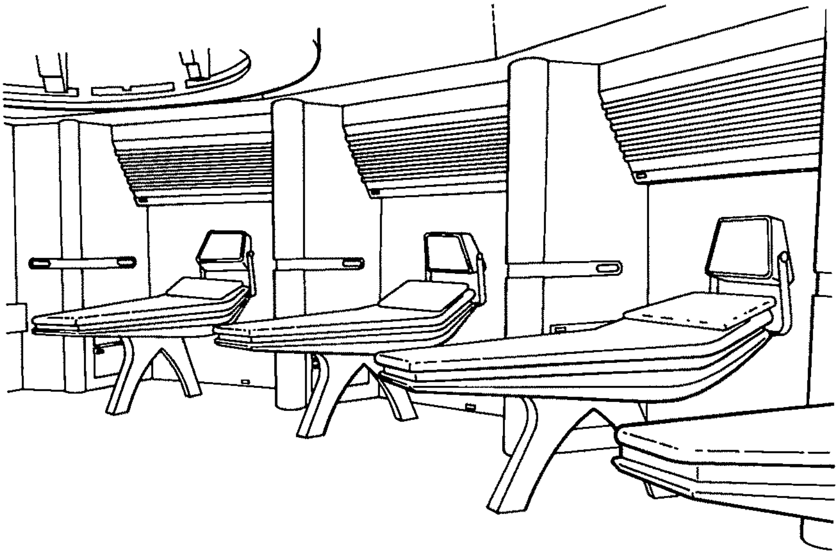

Figure 3. Deck 12 Sickbay intensive care ward, U.S.S. Enterprise. Can we get there from here? (*From* Sternbach R, Okuda M: Star Trek: The Next Generation Technical Manual. New York, Pocket Books, a division of Simon & Schuster, 1991, p 148; with permission.)

> [These sort of observations help] refute the dogma that discoveries come only from full-time scientists working at research institutions and demonstrate that inquisitive doctors can do research in any setting. . . . Doctors do detect many other clues, but they usually do not take the next steps of reporting the observation and starting studies to document the effect. Those are the crucial steps that help distinguish the gadfly from the true scientist.

VII

The future is bright; it offers considerable potential for the development of neuroanesthesia, not only as a practice but as an approach (Fig. 3). But *we* must set the agenda and not sit back and simply let progress come to us. To bring us forward into the twenty-first century, neuroanesthetists must harness the power of developing technologies and further apply our knowledge of acute patient care into both charted and uncharted realms of CNS injury.

Epilogue

Professor Jamais N. Pensepas motioned toward the door leading to the next room and it swished open.

"We lost a couple of patients in the early days, but the complication rate is now only about 0.1%, usually due to mild neuropsychiatric manifestations, thought by most authors to be due either to the particle gradient in the annular confinement beam or something to do with the phase-sequence linkage in the steering field."

Leading the students to the next procedure room, Pensepas turned and added, "However, some have attributed these complications to the anesthesia. . . ."

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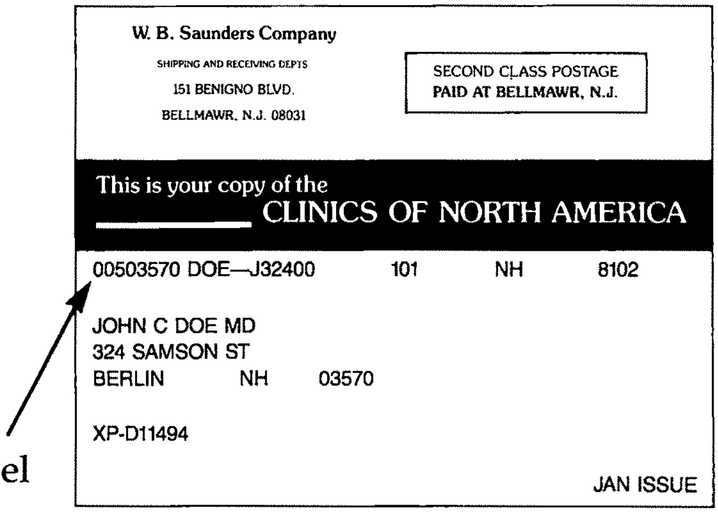

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